FORMULATION AND EVALUATION OF OSELTAMIVIR PHOSPHATE CAPSULES

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI – 600 032

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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APRIL-2012

ISO 9001 : 2008 Certified

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I **Register No. 26101007** hereby declare that this dissertation work entitled **"FORMULATION AND EVALUATION OF OSELTAMIVIR PHOSPHATE CAPSULES"** has been originally carried out by me under the supervision and guidance of Mr.N.Bala Krishna , M.Pharm. (industrial guide) and Mr. T. Udaya Kumar, M.Pharm., (institutional guide), Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai – 97 during academic year of 2011 – 2012. This work has not been submitted for any other degree at any other university.

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ACKONWLEDGEMENT

I express my fro found sense of gratitude to my esteemed guide **Mr. T. Udayakumar,** M.Pharm., Asst. professor, Department of Phamaceutics, C.L. Baid Metha college of Pharmacy, Chennai – 97, who gave inspiration and excellent guidance at every stage of my dissertation work, his constant encouragement valuable suggestions and discussions have enabled me to execute the present work successfully.

I shall remain indebted to Dr. Amarnath(F R&D manager),Mr.N. Bala krishna ,M.Pharm and Mr.D. Udhay kumar ,M.Pharm., (scientist in formulation R&D Department), in NATCO PHARMA LIMITED for having faith in me and helping me in carrying out the project work at their industry .Also I would like to thank R.chaitanya ,M.Pharm.,K. pavan,M.Pharm.,R. Dayanand,M.Pharm.,P. kiran,M.Pharm., for being so helpful to me in all aspects.I also express my thanks to my friends and classmates for their timely help and encouragement during my course and dissertation work.

I will express my love and soulful gratitude to **my family members** for their keen support and encouragement.

My humble thanks and prayer to the **Almighty,** who has given me the Strength, Confidence and Capacity to complete my work effectively

[Register No:26101007]

DEDICATED TO

MY

PARENTS AND MY FRIENDS

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LIST OF SYMBOLS AND ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
DT	-	Disintegration Time
%	-	percentage
°C	-	Degree Celsius
°F	-	Degree Fahrenheit
Ml	-	milliliter
Mg	-	milligrams
G	-	Grams
nm	-	nanometer
w/w	-	weight/weight
h/ml	-	hour/mililiter
UV	-	Ultra violet
FTIR	-	Fourier transform infrared spectroscopy
RH	-	Relative humidity
PVC	-	Poly vinyl cellulose
CDR	-	Cumulative drug release
Min	-	minute
FDA	-	Food and drug administration
ICH	-	International conference on harmonization
KBr	-	potassium bromide
IP	-	Indian pharmacopeia
JP	-	Japanese pharmacopeia
LOD	-	Limit of Detection

LOQ	- Limit of Quantification
RSD	- Relative Standard Deviation
RPM	- Revolutions per minute
HDPE	- High density Poly Ethylene
L	- litres
R.S	- Related substances

INTRODUCTION

Capsules[1]

The most versatile of all dosage forms is the capsule. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms in western medicine.

Definition:

Capsules are easier to swallow and are used by manufacturers when the drug can't be compacted into a solid tablet. They are also useful when the drug needs to be mixed with oil or other liquid to aid absorption in the body. It is normally a shell or container made of gelatin that contains the drug.

Explanation

A capsule is made of certain materials that stop the medication from dissolving in the acidic conditions of the stomach and the alkaline conditions of the small intestine. This is so the drug reaches the walls of the stomach/intestine and passes through into the blood stream.

Capsules are unit doses of drugs enclosed within soluble shells of gelatin or similar material, intended to be swallowed whole. Hard capsules were invented in 1833 in America. They were {and are today} made of gelatin and consist of two parts, a body and a lid [they were supplied readymade but were filled in the pharmacy].

Capsules are available in many different sizes and shapes and can be used for administration of powders, semisolids and liquids.

A capsule is a smooth, slippery, easy to swallow and tasteless shell of any convenient shape containing drugs. Capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opaquing agents, plasticizer and preservatives. (Leon Lachman 1991).

a) It is tasteless and particularly useful for drugs having unpleasant odour or taste.
b) It is economically produced in large quantities and has many pleasing colours.

c) It provides ready availability of the contained drug.
d) Manufacturing is easier as it uses minimal excipients and only little pressure is required while compacting as compared to tabletting.

Gelatin capsules[1] are an elegant and widespread pharmaceutical dosage form; they enable drugs to be easily and safely administered whether in liquid, paste or solid form. At the same time, pharmaceuticals in capsule form have a high degree of bioavailability. Pharmaceutical capsules enable active ingredients to be formulated with long shelf lives, protected from light and oxygen. Depending on the nature of the substance to be encapsulated, either hard- or soft capsules can be used. Soft capsules are the more suitable for liquid or paste fillings based on oil whilst hard capsules are used in general for powdered substances.

Types of capsules The main types of capsules are:

Hard gelatin capsules [2, 3] : The capsule shell The shell of hard gelatin capsules basically consists of gelatin, plasticizers and water. Modern day shells may, in addition, consist of preservatives, colours, opacifying agents, flavours, sugars, acids, enteric materials etc. The gelatin is marketed in a large number of varieties and a specific quality and gelatin having specified gel strength, viscosity, iron content etc. should be selected for capsules. The variations in gelatin properties arise because of changes in molecular weights and methods followed in conversion into gelatin. The average molecular weight of gelatin, varies between 20,000 and 2,00,000. Two popular grades of gelatin, Pharmagel-A and Pharmagel-B, are acid processed and alkali processed respectively. They have differing isoelectric points (Pharmagel-A: pH. 4.8 to 5.2, Pharmagel-B: ph 6.5 to 9.5). For capsule shells generally a mixture derived from pork skin and bones is used. Pork skin gelatin contributes plasticity while bone gelatin gives firmness. However, in using bone gelatin its calcium phosphate content should be watched since undue amounts can make capsules hazy. One important reason for the exclusive use of gelatin for making hard and soft capsules is its solubility characteristics in stomach fluids. It absorbs cold water readily, though the rate of absorption depends

upon moisture content of gelatin. Bloom Strength Bloom strength is an empirical gel strength measure, which give an indication of the firmness of gel It is measured by a bloom gelometer It determines the weight in grams required to depress a standard plunger a fixed distance into the surface of 6 2/3 % w/w gel under standard conditions Bloom strength in the range of 150-280 g are considered suitable for capsules.

The plasticizers used are glycerin, sorbitol etc. The exact proportions of gelatin and plasticizers have to be determined on the basis of the use of capsules and their storage conditions. Preservatives, if included, are generally a mixture of methylparaben (4 part) and propylparaben (1 part) to the extent of 0.2%. Flavours, if added, should not exceed 2% and are generally ethyl vanillin or essential oils. Sugar, if included, may be up to 5% of give the gelatin shell desirable chewable characteristics. The capsule shells are nowadays produced on mass scale by sophisticated machinery. Fundamentally speaking, in every machinery, pairs of pins corresponding to the bodies and the caps of the capsules are dipped in heated gelatin solutions containing the necessary additives. The dipping is followed by withdrawal of pins and their rotation a few times to distribute the solutions evenly. Cold air is simultaneously blown on the rotating pins to firm up the gelatin shells. These pins are, thereafter, passed though series of kilns with controlled rates of drying.

After drying, the bodies and caps are removed from pins by mechanical jaws and are trimmed to appropriate lengths by rotating blades. Finally the caps are placed on the bodies.

The capsules shells should be stored under controlled conditions of temperature and humidity. The normal moisture content of shell is 10 to 15%. Under conditions of low humidity they may soften and grow tacky. The shells for human use are marketed in 8 size depends upon its density and compressibility. Normally the shell manufacturers give a guidance of the approximate quantities of selected drugs that can be contained in different sizes.

Figure: 1 Hard gelatin capsules

Hard gelatin capsule manufacturing [2,3,4] (Loyd V. Allen, 2008)

1. Once raw materials have been received and released by Quality Control, the gelatin and hot demineralized water are mixed under vacuum in Stainless Steel Gelatin Melting System

2. After aging in stainless steel receiving tanks, the gelatin solution is transferred to stainless steel feed tanks.

3. Dyes, opacifants, and any needed water are added to the gelatin in the feed tanks to complete the gelatin preparation procedure. The feed tanks are then used to gravity-feed gelatin into the Capsule Machine.

6. The Pin Bars pass through the upper and lower kilns of Capsule Machine Drying System. Here gently moving air which is precisely controlled for volume, temperature, and humidity, removes the exact amount of moisture from the capsule halves.

7. Precision controls constantly monitor humidity, temperature, and gelatin viscosity throughout the production process

8. Once drying is complete, the Pin Bars enter the Table section which positions the capsule halves for stripping from the Pins in the Automatic section.

9. In the Automatic section, capsule halves are individually stripped from the Pins.

10. The cap and body lengths are precisely trimmed to a ±0.15 mm tolerance.

11. The capsule bodies and caps are joined automatically in the joiner blocks.

12. Finished capsules are pushed onto a conveyer belt which carries them out to a

container.

13. Capsule quality is monitored throughout the production process including size, moisture content, single wall thickness, and colour.

14. Capsules are sorted and visually inspected on specially designed Inspection Stations.

15. Perfect capsules are imprinted with the client logo on high-speed capsule printing machines. Capsules are now ready to be sterilized and packaged.

Soft capsules [1] :

The designation soft capsule implies that the outer wall contains, apart from gelatin, a plasticiser, the degree of softness and elasticity of which depends on the quantity and type of plasticizer used, the residual moisture and the thickness of the capsule wall. Soft capsules tend to have thicker walls than hard capsules. Glycerin and sorbitol, or a mixture of both, are normally used as plasticizers.

Figure 2 Soft gelatin capsules

Soft Gelatin Capsule Manufacturing [1,5,6]

In the manufacturing of soft gelatin capsules the capsulating process works in the following manner: warm liquid gelatin is spread over a slowly revolving stainless steel drum which is about 24" in diameter. This drum is exposed to 400 CFM of 57-59°F ir at 20% RH. The cool, dry air congeals the gelatin as the drum rotates so that a tacky, elastic band rolls off of the other end. This thin band is then automatically formed into capsules; filled with medicine, vitamins or other products; sealed; and dropped into a tray.

If the air blowing against the drum has too low a temperature, the gelatin will set too rapidly and become brittle which can cause the manufacturing process to grind to a halt. Too high of an air velocity will disturb the consistent thickness of the gelatin ribbon being formed. If the air temperature and humidity are too high, or the air velocity is too low, the gelatin will not solidify into a ribbon. Thus, the need for constant control of the air being introduced to the drum is critical in the process.

The extent of moisture to be removed during drying depends upon the size of the capsule, the number of capsules, and the period of time over which this moisture can be removed. Typically the environment to be maintained for effective and rapid drying corresponds to a dew point of 25° F or an absolute humidity level of 20 grains per pound of air.

Table: 1 Typical design conditions for manufacturing of soft gelatin capsules

Temperature	Humidity
78°F	15% RH
68°F	20% RH

In order to achieve the controlled air requirement listed above, refrigeration equipment alone becomes uneconomical, impractical and cumbersome to design, operate and maintain. On the other hand desiccant type dehumidifiers combined with refrigeration can offer a simple and economical solution to controlling both temperature and humidity levels as low as necessary.

Dry-Air desiccant dehumidifiers have been utilized in many capsulating and soft gel manufacturing applications all over the world resulting in millions of dollars saved annually.

Table: 2 Different capsule sizes and their capacities

Size	Outer diameter(mm)	Height/locked length (mm)	Actual volume (ml)
000	9.97	26.14	1.37
00	8.53	23.30	0.95
0	7.65	21.70	0.68
1	6.91	19.40	0.50
2	6.35	18.00	0.37
3	5.82	15.90	0.30
4	5.31	14.30	0.21
5	4.91	11.10	0.13

Limitations:

Capsules are not suitable for drugs that are very soluble, such as the salts (potassium chloride, potassium bromide, ammounium chloride). In these situations, the fluid penetrating the capsule rapidly dissolves the salt and creates a high concentration solution, which can cause nausea and vomiting when it contacts the gastric mucosa.

Strongly efflorescent or deliquescent materials are not suitable for capsules since efflorescent materials may cause capsules to soften when water is lost and strongly deliquescent materials may make the capsule shell brittle when the moisture is extracted from the shell into the powder.

Manufacturing operation of capsules[1]

The manufacturing operations can be broadly divided into four broad phases of :

a) Drug Preparation
b) Capsule filling
c) Capsule finishing

d) Capsule packaging

a) Drug preparation:

The drug usually is in powder form, pellet form, tablet form or combination of any of them.

b) Capsule filling:

The capsule body and cap are separated, drug filled accurately and capsule body and cap are joined together to produce the filled capsule. Hand filling, hand filling with loader, semi-automatics machines and automatic machines are used for above purpose.

c) Capsule finishing:

The major operations are de-dusting / polishing, sorting, counting and inspection. Filled capsules require some sort of dusting and/or polishing operations, particularly if powder filling is done. This operation may be based on the type of filing equipment used, the type of powder used for filling and individual desire for finished appearance of capsules.

There are four methods used for de-dusting:

a) Pan polishing
b) Cloth dusting or towel polishing
c) Brushing (with vaccum)
d) Belt polishing (with vaccum)

Sorting

Sorting is an operation of segregating defective, under filled, over filled and broken open etc capsules from the proper capsules. It is usually done visually and may be aided by mechanical means like conveyer belts, air flow deflectors etc. it may be online or offline. Counting of capsules may be done by machine while filling or manually. Mechanical counters are used in manual counting.

Usually bottle filling blister packing and strip packing machines include automatic counters. Single or double snap capsules coupled with blister packing etc gives reasonable pilfer proofing. Printing of capsules is done by capsule manufacturers. Printing machines operate on a rotogravure process and printing may be longitudinal or circumferential, and in different colours. Only approved colours under drugs act are used.

d) Capsule packing:

Comprises of packing and sealing capsules in bottles, blisters and strips.

Bottle packing is resorted for large unit size (e.g. say more than 100 capsules for unit pack. Semiautomatic bottle filling machines with conveyer belt and associated work stations of labeling, stoppering, capping and sealing are available and indigenously and used. Most widely used bottles are glass bottles. A line here may comprise of 7-12 persons).

Strip packing may use paper poly, glassine poly or aluminum poly. Paper poly is the cheapest material but is not being used. Glassine poly and aluminum poly offer better product protection against moisture etc and aluminum poly is substantially used by the industry. The thickness of packing materials varies marginally.

Now a days the trend is to use blister packing**,** it has lid foil of thermoforming PVC, PVC with PVDV and base foil of aluminum. It results into considerable saving of packing material, has better aesthetic appeal and is convenient for patient compliance, initial investment is however, higher.

Secondary packing comprises of carton packing, strapping and labelling, Defoiling is an operation of opening rejected strips/ blisters and claiming OK capsules. Defoilers are available indigenously. Most, widely used method however is manual.

Encapsulation process[1]

Two general methods are: Individual hand filling and capsule machine filling.

Hand filling

The powder is arranged on a suitable surface with spatula so that the thickness of the pile is about 2/3 the length of the capsule body. This is to avoid contacting the powder with the hands when punching capsules. The use of gloves or finger cots is recommended to minimize contact with the powder and to avoid finger prints on the capsules. Another option is to use of cap from a second capsule slipped over the base of a capsule to be filled as a holder while punching. Using this technique, capsules do not touch the compounding pharmacist's hands. The capsule is pressed into the powder with slight rotation as it enters the power and reaches the working surface to aid in packing the powder. When the capsule becomes full, a slight resistance can be felt as the capsule is pressed through the powder.

An alternative hand filling method involves blocking and dividing the powder into individual portions for each capsule. This approximation is not very accurate and is not recommended. To pack powder that will not stick in the capsules when punching, place each capsule base on its side and use a spatula to guide or fill the powder. Care must be exercised so that the capsule is not scraped or scratched. Granular materials are particularly difficult to punch into capsules because they are not very cohesive. Reducing the particle size to the point at which the powders stick together may alleviate this problem.

Capsule filling device [1,7]

A number of different manually operated capsule filling devices are commercially available for filling up to 50 to 100 capsules at a time. These machines can be used for preparing smaller quantities of capsules by blocking off unused holes with an index card. The method of using these machines requires a careful determination of the capsule formation. The powder is blended as previously discussed. Empty gelatin capsules are placed into the device and oriented so that the cap is on top. The machine is

worked to separate the base form the cap and the portion of the machine holding the caps is removed and set aside. The capsule bases are allowed to drop into place so that the tops are flush with the working surface.

The powder mix is spread the powder uniformly and evenly into the capsule bases or the machine can be tapped to spread the powder and drop it down into the capsule bases. A small device consisting of several pegs on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is spread evenly over and into the capsule bases and tamped. These procedures are repeated until all of the powder is in the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a cleaned cloth, and packaged.

Hard gelatin capsules have been around for over 50 years and the range of filling machines to go with this is of a similar vintage. Powders with a Carr's Index greater than 25% are more appropriate for the dosator than for a tamping system and those of less than 15% are more appropriate, in general, to the tamping ping.

These are other criteria, which are important too, such as material particle size distribution and melting point. Over the past 20 years, increasingly accurate capsule weighers have been developed, with the modern ones using digital intelligent weight cells capsules of weighing the capsule several times, and using the average to give an accuracy of about 1-2mg. But, despite the best efforts of capsule shell manufacturers, limitations of the gelatin itself are such that the weight tolerance on an empty capsule becomes significant at low fill weights. For example, even on a capsule size 0 capsule weighing 96mg, the weight tolerance is ±6mg. Currently, even when weighing empty capsules before using them on the capsule filer struggles to cope with the low fill weights.

Filling mechanisms

1.Auger fill

Encapsulator wherein the powder / formulation is driven into the capsule bodies by means of a rotating auger.

2.Vaccum Fill

Encapsulator wherein the powder / formulation is drawn by means of vacuum into cylinders containing porous pistons. The powder is scrapped flush with the open end of the cylinders, and then ejected into the capsule bodies via pressurized air through the porous piston.

3.Vibratory fill

Encapsulator wherein a perforated plate is vibrated in the bed of the powder / formulation. The vibratory action facilitates powder flow into the capsule bodies through holes in the plate.

4.Dosing disk

Encapsulator wherein cylindrical dosing tubes fitted with movable pistons are plunged into the powder / formulation bed to form soft powder plugs., The powder plugs are then pushed by the pistons from the dosators into the capsule bodies.

Powder fill

1.Acco fill

Powder is charged into a hopper and is preconditioned by mixing and / or agitator blade(s) to assist powder deliver and flow.

The pre-determined amount of the powder is drawn into the fill wheel ports with vacuum from the supply hopper. The powder is held by the vacuum in the fill wheel ports until it is indexed into and dispensed into the container by use of compressed air.

2.Auger

Powder is charged into the hopper and is pre-conditioned by mixing and / or agitator blade (s) to assist powder delivery and flow. An auger is utilized to deliver the powder from the hopper into the container using a predetermined degree of revolution.

FILLING OPERATIONS

Empty capsules

Empty capsules are sold by sizes.the ones most commonly employed for human use range from size 0,the largest,to size 5,the smallest.size 00 capsules may occasionally be required because of the volume of material to be filled,but this size is not used commercially in large volume.although capsules change dimensions to some extent with varied moisture content and conditions encountered before use,capsules as received from the supplier generally have moisture content between 12 and 15% and these levels are maintained during storage in the original container.storage under high temperature conditions(above 100°F)must not be prolonged.exposure to high or extremely low humidity conditions for extended periods after the containers are opened causes the capsules to either gain or lose moisture .at high moisture levels,the capsules absorb moisture,and may soften and become tacky.in severe cases,the capsules may absorb moisture,to cause them to deform under their own weight.At low moisture levels,they become brittle and suffer dimensional changes,which may cause handling problems in the filling equipment.

Regarding the empty capsules only, handling is ideally carried on in areas within the relative humidity range of approximately 30 to 45%, since major moisture content changes do not occur within these limits. If conditions drier than these are necessitated because of the ingredients being filled,exposures of the empty capsules prior to filling should be minimized.strong consideration should be given to the use of air conditioned facilities to control both temperatures and humidity when high- speed filling equipment is being operated.

SPECIAL TECHNIQUES

Some special techniques that may be applied to the capsules as a dosage form include the following.

1.Imprinting is a convenient method by which company and/or product identification information can be placed upon each capsule.The imprinting operation is best performed on the empty capsules,although filled capsules can be printed.The preference

for imprinting empty capsules arises from the fact that the imprinting operation may occasionally damage some capsules.when filled capsules arises from the fact that the imprinting operation may occasionally damage some capsules.When filled capsules are imprinted,contamination,poor print quality,and actual damage to the imprinting equipment result.Various types and capacities of equipment are commercially available for this purpose in the united states.

Hartnett offers a variety of machines with out-puts as high as 50,000 capsules per hour.Also available is a unit that prints around the circumference of the capsules,as opposed to a longitudinal imprint,however,this machine operates at a slower rate.A lower- capacity unit(up to 250,000 capsules per hour)allows printing on both sides of the capsule,In different colours if desired

Markem offers three models,which range from approximately 60,000 to 250,000 capsules per hour.all three models allow for two-sided printing,

Ackley offers a straight- line imprinter with an output rate of about 50,000 capsules per hour.

In addition,several firms,including the major empty capsule supplier,offer custom imprinting services.

All imprinting machines operate on a rotogravure process,and a wide variety of colors of edible inks ,both water-and solvent-based, are commercially available.

2.special purpose capsules are capsules to which a special treatment has been given in an attempt to retard the solubility in some manner .this may be done in an attempt to delay absorption of the active ingredient, or to provide enteric properties. Normal solubility for gelatin capsules, either empty or filled,is not defined.However, the general service administration ,in federal specification ,defines solubility limits for capsules as follows(a)water resistance-fails to dissolve in water at 20 to 30°c in 15 min(b)acid solubility-dissolves in less than 5min in 0.5%aqueous HCL(w/w)at 36 to 38°c.

None of the following is used for any commercial products as far as is known and cannot be seriously recommended except for experimental purposes, because of generally unpredictable results.

a. Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapours or treatment with aqueous formalin results in an unpredictable decrease in solubility of the gelatin film,owing to cross-linkage of the gelatin molecule initiated by the aldehyde. This result may also be noted if the product being filled contains aldehydic materials are added. Because of the nature of reaction, it is difficult to control the degree of insolubilisation,or indeed,to prevent ultimate complete solubility.

b. Various coatings have been used in an effort to provide similarly modified solubility characteristics.These coatings include salol, shellac,cellulose acetate phthalate and certain resins that have usually been applied by pan coating techniques.

Gelatin capsules do,however,provide a convenient way to deliver pellets or granular material when delayed or prolonged release properties have been incorporated in all or portions of the material to be filled.

3.separation of incompatible materials is carried out by the use of a two-phase fill in the capsule.one phase consists of either a soft capsule,a smaller hard capsule,a pill,or a suitably coated tablet that is filled in to each capsule.following this as a second phase,a powder fill is added in the usual manner.If this technique is used on commercial filling equipment,modification must be made to the filling cycle of the machine.These changes would include,at minimum,the necessary changes in the machine operation to allow materials to be loaded at two points during the filling cycle.

4.Recently there has been a revival of interest in the filling of conventional two-piece gelatin capsules with liquids and semisolids.Hard gelatin capsules were commonly used as early as 1890s for oils,ethereal extracts,and pill masses,but the ability to fill the capsules on semiautomatic and automatic equipment is a recent development.The ```formulations used for filling are usually semisolids at ambient temperatures,which are melted to allow filling.or they are thixotropic formulations in which the shear developed in filling allows pumping,but whose high viscosity when shear is absent

prevents leakage after filling.Quantitative assessment of the gastric emptying of hard gelatin capsules filled with thixotropic liquids can be made in terms of the lag time prior to emptying, and the slope of the first order emptying curve.

INFLUENZA

Commonly referred to as the **FLU,** is an infectious disease caused by RNA viruses of the family orthomyxoviridae(the influenza viruses),that effects birds and mammals .The most common symptoms of the disease are chills, fever. sorethroat, musclepains. severe headache, coughing ,weakness ,discomfort.

Although it is confused with other influenza-like illnesses ,especially the common cold ,influenza is a more severe disease than the common cold caused by different type of virus.

Influenza may produce nausea and vomiting, particularly in children , but these symptoms are more common in the unrelated gastroenteritis ,which is sometimes, inaccurately referred to as "stomach flu". Flu can occasionally cause either direct viral Pneumonia or direct bacterial pneumonia.

Typically influenza is transmitted through the air by coughs or sneezes, creating aerosols containing the virus. Influenza can also be transmitted by direct contact with bird droppings or nasal secretions ,or through contact with contaminated surfaces. Airborne aerosols have been thought to cause most infections, although which means of transmission is most important is not absolutely clear. Influenza viruses can be inactivated by sunlight ,disinfectants and detergents .As the virus can be inactivated by soap, frequent hand washing reduces the risk of infection.

Influenza spreads around the world in seasonal epidemics, resulting in deaths of between 250,000 and 50,000 people every year ,up to millions in some pandemic years .On average 41,400 people died each year in the united states between 1979 and 2001 from influenza

Three influenza pandemics occurred in the 20 century and killed tens of millions of people, with each of these pandemics being caused by the appearance of a new strain of the virus in humans .Often, these new strains appear when an existing flu virus spreads from humans to other animal species ,or when an existing human strain pricks up new genes from a virus that usually infects birds or pigs .An avian strain named H5N1 raised the concern of new influenza pandemic, after it emerged in Asia in 1990s,but it has not evolved to a form that spreads easily between people. In April 2009 a novel flu strain evolved that combined genes from human pig, and bird flu, initially dubbed "SWINE FLU" and also known as influenza A/H1N1 emerged in Mexico, the united states and several other nation .

The world health organization officially declared the outbreak to be pandemic on june11, 2009. The WHO's declaration of a pandemic level 6 was an indication of spread, not severity, the strain actually having a lower mortality rate than common flu out breaks.

Vaccinations against influenza are usually made available to people in developed countries. Farmed poultry is often vaccinated to avoid decimation of the flocks. The most common vaccine is the trivalent influenza vaccine (TIV) that contains purified and inactivated antigens against three viral strains. Typically, this vaccine includes, material from two influenza A virus subtypes and one influenza virus B strain .the TIV carries no risk of transmitting the disease ,and it has very low reactivity .A vaccine formulated for one year, may be ineffective in the following year ,since the influenza virus evolves rapidly, and new strains quickly replace the older ones. Antiviral drugs such as neuraminidase inhibitor OSELTAMIVIR have been used to treat influenza.

Table:3 SIGNS AND SYMPTOMS

Symptom	Sensitivity	Specificity
Fever	68-86%	25-73%
Cough	84-98%	7-29%
Nasal	68-91%	19-41%

Congestion :

Symptoms of influenza can start quite suddenly one to two days after infection.Usually the first symptoms are chills or a chilly sensation,but fever is also early common in the infection,with body temperatures ranging from 38-39°c.Many people are so ill that they are confined to bed for several days with aches and pains throughout their bodies,which are worse in their backs and legs.Symptoms of influenza include:

- Fever and extreme coldness
- Cough
- Nasal congestion
- Bodyaches, especially joints and throat
- Fatigue
- Headache
- Irritated,watering eyes
- Reddened eyes,skin(especially face)mouth,throat and nose
- Petechial rash
- In children,gastrointestinal symptoms such as diarrhea and abdominal pain

It can be difficult to distinguish between the common cold and influenza in the early stages of these infections,but a flu can be identified by a high fever with a sudden onset and extreme fatigue.diarrhea is normally not a symptom of influenza in adults,although it has been seen in the some human cases of the H5N1 "bird flu"and can be a symptom in children

Since antiviral drugs are effective in treating influenza ,if given early, it can be important to identify cases early .of the symptoms listed above, the combinations of fever with cough. Sore throat and/or nasal congestion can improve diagnostic accuracy. Two decision analysis studies suggest that during local outbreaks of influenza, the prevalence will be over 70%,and thus patients with any of these combinations of symptoms may be treated with neuraminidase inhibitors without testing .Even in the

absence of a local outbreak, treatment may be justified in the elderly during the influenza season as long as the prevalence is over 15%.

The available laboratory tests for influenza continue to improve. The United States Centers for Disease Control and Prevention maintains an up-to-date summary of available laboratory tests

In virus classification Influenza viruses are RNA viruses that make up three of five genera belonging to the paramyxo virus family that are a common cause of respiratory infections in children such as croup,but can also cause a disease similar to influenza in adults.

Influenza virus A

This genus has one species, influenza A virus. wild aquatic birds are the natural hosts for a large variety of influenza A, occasionally, viruses are transmitted to other species and may then cause devastating outbreaks in domestic poultry or give rise to human influenza pandemics. The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. The influenza A virus can be subdivided in to different serotypes based on the antibody response to these viruses. The serotypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:

- H2N2, which caused Asian Flu in 1957
- H1N1, which caused Spanish Flu in 1918 and Swine Flu in 2009
- H3N2,which caused Hong Kong Flu in 1968
- H5N1, which caused Bird Flu in 2004
- H7N7, which has unusual zoonotic potential
- H1N2, endemics in humans pigs and birds

Influenza virus B

This genus has one species, influenza B virus. Influenza B almost exclusively infects humans and is less common than influenza A.This type of influenza mutates at a rate 2-3 times slower than type A and is consequently is less genetically diverse,with only one influenza B serotype.

Influenza virus C

This genus has one species,influenza C virus,which infects humans ,dogs and pigs, sometimes causing both severe illness and local epidemics.However, influenza C is less common than the other types and usually only causes mild disease in children

Infection control

Reasonably effective ways to reduce the transmission of influenza include good personal health and hygienic habits such as not touching your eyes ,nose or mouth, frequent hand washing, covering coughs and sneezes, avoiding close contact with sick people, smoking raises the risk of contracting influenza, as well as producing more severe disease symptoms.

Since influenza spreads through both aerosols and contact with contaminated surfaces. Alcohol is an effective sanitizer against influenza viruses, people with flu are advised to get plenty of rest, drink plenty of liquids. avoid using alcohol and tobacco. The two classes of antiviral drugs used against influenza are neuraminidase inhibitors and M2 protein inhibitors. Neuraminidase inhibitors are

Neuraminidase inhibitors

Antiviral drugs such as oseltamivir (trade name tamiflu) and zanamivir(trade name relenza) are neuraminidase inhibitors that are designed to halt the spread of virus in the body .These drugs may be effective against influenza A and B. Different strains of influenza viruses have differing degrees of resistance against these antivirals ,and it is impossible to predict what degree of resistance a future pandemic strain might have.

M2 inhibitors

The antiviral amantadine and rimantadine block a viral ion channel and prevent the virus from infecting cells.These drugs are effective against influenza A.Measured resistance to amantadine and rimantadine in American isolates of H3N2 has increased to 91%.This high level of resistance may be due to easy availability of amantadines.

Uncomplicated influenza is characterized by the abrupt onset of constitutional and respiratory signs and symptoms.However,in some persons,influenza can exacerbate underlying medical conditions or lead to secondary bacterial pneumonia.Epidemics of influenza occur during the winter months nearly every year .The main method for preventing influenza and its more severe complications is immunoprophylaxis with inactivated vaccine. Influenza specific antiviral drugs for chemoprophylaxis are an important adjunct to vaccine,but they are not a substitute for influenza vaccine.four antiviral agents are approved for preventing influenza

Amantadine and rimantadine are chemically related antiviral drugs active against influenza A virus but not influenza B virus .After influenza A viruses enter cells ,these drugs inhibit the uncoating of influenza A viruses by blocking the ion-channel activity of the viral M2 protein

U.S.Food and drug administration are new members of a new class of antiviral agents that selectively inhibit the neuraminidase of both influenza A and B viruses .Neuraminidase inhibitors are analogues of sialic acid. Their proposed mechanism of action is to block the active site of neuraminidase and leave uncleaved sialic acid residues on the surfaces of host cells and influenza viral envelopes. Viral hemagglutinin binds to the uncleaved sialic acid residues, the result is viral aggregation at the host cell surface and a reduction in the amount of virus that is released and can infect other cells

NA inhibitor-resistant viruses were thought to not readily emerge ,yet studies have demonstrated a higher prevalence of oseltamivir-resistant viruses than was expected among oseltamivir- treated patients.

Emergence of influenza viruses with reduced susceptibility to neuraminidase inhibitors(NAIS) develops at a low level following drug treatment, and person-to-person transmission of resistant virus has not been recognized to date. The neuraminidase inhibitor susceptibility network was established to follow susceptibility of isolates and occurrence of NAI resistance at a population level in various parts of the world .Isolates from the WHO influenza collaborating centers were screened to susceptibility to oseltamivir and zanamivir by a chemiluminescent enzyme inhibition assay,and those considered potentially resistant were analyzed by sequence analysis of the neuraminidase genes.

Viruses are the ultimate expression of parasitism they not only take nutrition from the host cell but also direct its metabolic machinery to synthesis new virus particles.Virus directed enzymes have been identified in the infected cell and some viruses have few enzymes of their own which may have higher affinities for some anti metabolites or inhibitors than the regular cellular enzymes. A virus is made up of a nucleic acid core enclosed in a protein coat called capsid which consists of repeating, identical subunits. Certain other constituents protect this nucleic acid moiety from the action of various body fluid enzymes.Viruses,unlike bacteria,have no cell wall,most viruses survive outside the host cell only for a short time, the major difficulties involved in viral infections.

- A drug which acts on a virus in the cytoplasm may not necessarily act on a virus that multiplies in the nucleus
- The severity of infection produced by a virus and its response to a given drug differ considerably in different species
- Precise diagnosis of many virus infections is difficult,further invitro efficacy of a new drug may not predict its therapeutic efficacy.
- The antiviral compounds are likely to be most effective during the stage of multiplication of virus,which is difficult to detect. Viruses undergo structural changes and develop drug resistance.

- Unlike most antibiotics,antiviral drugs donot destroy their target pathogen, instead they inhibit their development.
- Antivirals also can be found in essential oils of some herbs.
- The emergence of antivirals is the product of a greatly expanded knowledge of the genetic and molecular functions of organisms,allowing the biomedical researchers understand the function and structure of viruses

Human H1N1 and H3N2 influenza A viruses are highly contagious and cause "seasonal influenza world wide.Although human-to-human transmission is rare, once the H5N1viruses acquire the ability, a devastating pandemic may be inevitable.

Two countermeasures are available to control human influenza:Vaccination and antiviral treatment. Although vaccination plays a critical role in prophylaxis, it makes more than six months to produce sufficient vaccine to cover a large proportion of the human population upon the emergence of a new strain.Therefore, antivirals are important tool to mitigate an influenza pandemic.

2. LITERATURE REVIEW

Hoffmann-La Roche *et al* (2010).,[15] Influenza is a transmissible viral pathogen that continues to cause substantial morbidity and mortality. Oseltamivir is an orally administered antiviral medication that selectively inhibits the influenza neuraminidase enzymes that are essential for viral replication. Treatment of infected children > or =1 year and adults of all ages may decrease the severity and duration of the symptoms of infection, while prophylactic dosing can prevent their onset. Oseltamivir is ingested in the form of a prodrug (oseltamivir phosphate) that is rapidly converted by hepatic esterases into the active metabolite, oseltamivir carboxylate. Oseltamivir carboxylate has high bioavailability and penetrates sites of infection at concentrations that are sufficient to inhibit viral replication. The pharmacokinetics of oseltamivir and oseltamivir carboxylate are dose proportional after repeated doses of up to 500 mg twice daily. This predictable profile means that oseltamivir is suitable for use in diverse patient populations, which may include young children and elderly patients, various ethnic groups and those with renal or hepatic impairment. As the potential for drug interactions is low, oseltamivir is also suitable for use in patients with co-morbid conditions who are likely to be receiving concomitant medications.

Osato H *et al* (2010).,[16] An efficient formal synthesis of oseltamivir phosphate (Tamiflu) has been achieved in 12 steps with use of the inexpensive and highly abundant D-ribose as the starting material. This concise alternative route does not utilize protecting groups and features the introduction of 3-pentylidene ketal as the latent 3-pentyl ether, the use of a highly efficient rcm reaction to form the Tamiflu skeleton, and selective functional group manipulations

Lindemann L *et al* (2010).,[17] Neuropsychiatric adverse events have been reported in influenza patients with and without exposure to oseltamivir (Tamiflu), triggering speculation as to whether oseltamivir may be interacting with any human receptors and contributing to such neuropsychiatric events. In this study, the in vitro selectivity profile

of oseltamivir prodrug and active metabolite was investigated. Both compounds lacked clinically relevant pharmacological activities on human, rodent and primate neuraminidases and on a panel of 155 other molecular targets, including those relevant for mood, cognition and behavior. Neuropsychiatric adverse events observed in influenza patients are likely a phenomenon caused by the infection rather than by oseltamivir.

Laborde-Kummer E *et al* (2009).,[18] A rapid and reliable capillary zone electrophoresis method was developed and validated for the assay of oseltamivir phosphate in capsules. Separation was carried out in fused silica capillary (60.2 cm total length and 10.0 cm effective length, 75 microm i.d.) by applying a potential of -15 kV at 25 degrees C. The selected electrophoretic buffer consisted of 50 mM sodium phosphate, pH 6.3 (direct UV detection, 226 nm). A short electrophoretic analysis time (less than 1.5 min) was obtained using the short end injection mode. The method was validated in terms of specificity, linearity, precision and accuracy. The RSD values were 0.94 and 0.98% for repeatability and intermediate precision, respectively. Recovery determinations allowed the calculation of a confidence interval from 98.64 to 100.26% with a relative standard deviation value of 0.38%. LOD and LOQ were estimated at 0.97 and 3.24 microg/mL, respectively. The validated method was successfully applied to the determination of oseltamivir in three commercially available capsules (Tamiflu, Saiflu and Flufy). The results were in good agreement with those obtained by a HPLC method previously developed in our laboratory. This method presents advantages including short run time, simple and rapid sample preparation and no use of non-aqueous solvent throughout the analysis.

Ogihara T *et al* (2009).,[19] Oseltamivir, an ester-type prodrug of the neuraminidase inhibitor[3R,4R,5S]-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (Ro 64-0802), has been developed for the treatment of A and B strains of the influenza virus but has neuropsychiatric and other side effects. In this study, we characterized the transport across intestinal epithelial cells and the absorption

of oseltamivir in rats. Uptake by Caco-2 cells (human carcinoma cell line) and HeLa cells transfected with peptide transporter 1 (HeLa/PEPT1) was time- and temperature-dependent and was inhibited by typical PEPT1 inhibitors such as glycyl-sarcosine (Gly-Sar). The uptake by Caco-2 cells and HeLa/PEPT1 was saturable, with similar K(m) values. Oseltamivir absorption in adult rats was greatly reduced by simultaneous administration of milk, casein, or Gly-Sar. Furthermore, the plasma and brain concentrations of oseltamivir were higher in fasting than in non fasting rats after oral administration. These results suggest that oseltamivir is a substrate of PEPT1 and that PEPT1 is involved in its intestinal absorption.

Nie LD *et al* (2009).,[20] Oseltamivir phosphate (1) was synthesized from (-)-shikimic acid through a short and practical synthetic route via eight steps in 47% overall yield. In addition, the highly regioselective and stereoselective nucleophilic replacement of OMs by the N(3) group in the third and seventh steps has been studied in detail, and the reaction conditions were optimized.

Aydoğmuş Z *et al* (2009).,[21] A new, simple and sensitive spectrofluorimetric method has been developed for the determination of oseltamivir phosphate (OSP) in capsules. The method is based on the reaction between oseltamivir and fluorescamine in borate buffer solution of pH 8.50 to give highly fluorescent derivatives that are measured at 483 nm using an excitation wavelength of 381. The different experimental parameters effecting the development and stability of the reaction product were carefully studied and optimized. The fluorescence intensity concentration plot is rectilinear over the range 50-450 ng mL(-1) with a lower detection limit (LOD) of 1.219 ng mL(-1) and limit of quantitation (LOQ) of 4.064 ng mL(-1). Selectivity was validated by subjecting stock solution of OSP to acidic, basic, oxidative, and thermal degradation. No interference was observed from excipients present in formulations. The developed method was successfully applied to determination of the drug in capsules. The mean % recovery (n = 6) was 100.08. The results obtained were in good agreement with those obtained using a reported spectrophotometric method.

Gong J *et al* (2008).,[22] Oseltamivir phosphate (Tamiflu) is the only orally active anti-influenza drug that potently inhibit neuraminidase. The recent emergence of avian flu, especially the H5N1 type, makes the situation of Tamiflu supply and demand increasingly serious. Further optimization of the current commercial approach and exploration of new synthetic routes are urgent. Here, different synthetic strategies of oseltamivir phosphate are reviewed, including discovery and improved synthetic route from (-)-quinic acid or (-)-shikimic acid, new asymmetric synthesis via catalytic desymmetrization of a meso-aziridine (CDMA), Diels-Alder Reaction and from other available materials.

Zutter U *et al* (2008).,[23] A new, enantioselective synthesis of the influenza neuraminidase inhibitor prodrug oseltamivir phosphate 1 (Tamiflu) and its enantiomer ent-1 starting from cheap, commercially available 2,6-dimethoxyphenol 10 is described. The main features of this approach comprise the cis-hydrogenation of 5-(1-ethyl-propoxy)-4,6-dimethoxy-isophthalic acid diethyl ester (6a) and the desymmetrization of the resultant all-cis meso-diesters 7a and 7b, respectively. Enzymatic hydrolysis of the meso-diester 7b with pig liver esterase afforded the (S)-monoacid 8b, which was converted into cyclohexenol 17 via a Curtius degradation and a base-catalyzed decarboxylative elimination of the Boc-protected oxazolidinone. Introduction of the second amino function via S(N)2 substitution of the corresponding triflate 18 with NaN3 followed by azide reduction, N-acetylation, and Boc-deprotection gave oseltamivir phosphate 1 in a total of 10 steps and an overall yield of approximately 30%. The enantiomer ent-1 was similarly obtained via an enzymatic desymmetrization of meso-diester 7a with Aspergillus oryzae lipase, providing the (R)-monoacid ent-8a.

Ono H *et al* (2008)., [24]Oseltamivir phosphate (Tamiflu), an anti-influenza virus drug, is hydrolyzed by carboxylesterase to an active metabolite. The metabolite inhibits the influenza virus-specific neuraminidase. In this study, the effects of oseltamivir on normal core body temperature were studied in mice. Oseltamivir (30-300 mg/kg, intraperitoneally (i.p.) and 100-1000 mg/kg, orally (p.o.)) dose-dependently lowered the body temperature. The effects of oseltamivir (p.o.) continued longer than those of oseltamivir (i.p.), and approximately triple doses of oral oseltamivir were needed to

produce the same peak effects as intraperitoneal oseltamivir. The non-steroidal anti-inflammatory drug diclofenac (1-30 mg/kg, i.p.) did not affect body temperature, and (at 30 and 60 mg/kg, s.c.) did not interact with the hypothermic effects of oseltamivir (100 mg/kg, i.p.). Zanamivir, which also inhibits neuraminidase, did not produce hypothermia at doses of 100 and 300 mg/kg, i.p. Clopidogrel (100, 300 mg/kg, i.p.), which is metabolized by the same carboxylesterase, tended to decrease the hypothermic effects of oseltamivir (100 mg/kg, i.p.). These results suggest that the hypothermic effects of oseltamivir are due to its hydrolytic metabolite, and that the hypothermia observed in mice has some relationship to the antipyretic effects and severe hypothermia (adverse event) observed in influenza patients after taking oseltamivir.

Gholamreza Bahrami *et al* (2008).,[25] This study was aimed at developing a fast and sensitive method for determination of oseltamivir carboxylic acid (OCA), the active moiety of anti influenza agent, oseltamivir phosphate, in human serum by high performance liquid chromatography and UV detection. The analyte and an internal standard (vanillin) were extracted from human serum by a solid phase extraction (SPE) procedure. Chromatographic separation was achieved using reverse phase C18 column with a mobile phase consisting of 0.05M phosphate buffer containing triethylamine (1 mL/L; pH 3.0) and acetonitrile (70:30, v/v). The detection wavelength was set at 215 nm. The average recoveries of the drug and internal standard were 98 and 85%, respectively. The calibration curve was linear over a concentration range of 15–6400 ng/mL of OCA in human serum. The lower limits of detection and quantification were 5 and 15 ng/mL, respectively. The coefficient variation values of both inter- and intra-day analysis were less than 12% whereas the percentage error was less than 4.5. The stability of the drug at the serum samples maintained at −40 ◦C for 60 days was found to be 100% from the initial value and no interferences were found from either endogenous components in serum or commonly co-administrated antiviral drugs. The validated method was applied to a randomized cross-over bioequivalence study of two different oseltamivir phosphate preparations in 24 healthy volunteers.

Aoki FY *et al* (2007).,[26] Oseltamivir phosphate is a prodrug of oseltamivir carboxylate, a highly specific inhibitor of influenza virus neuraminidases. Given that oseltamivir carboxylate binds to highly conserved, essential amino acids in the catalytic site of the enzyme, and that the activity of neuraminidase is critical for virus release from infected cells and subsequent virus spread, the drug was expected to have a low propensity to select for viable resistant mutants. Indeed, viruses with neuraminidase (and haemagglutinin) substitutions conferring reduced susceptibility to oseltamivir have been generated with difficulty in vitro, and these mutants generally have reduced infectivity and transmissibility compared with wild-type virus in animal models. Studies of seasonal influenza isolates collected before the introduction of oseltamivir show an absence of naturally occurring resistance. Few resistant mutants have arisen during clinical trials of oseltamivir in seasonal influenza, with cumulative data from all Roche-sponsored studies indicating an incidence of resistance of 0.32% in adults (0.4%, including low-level mutants detected by genotyping alone in mixed virus populations) and 4.1% (5.4%) in children. Higher incidences of resistance were observed in two small Japanese studies, in which children received a different dosing schedule from their Western counterparts. In summary, the overall incidence of influenza virus resistance associated with the seasonal use of oseltamivir is currently low and resistant viruses might be of little clinical significance, except perhaps in immune compromised individuals. However, continued vigilance, especially of emerging avian H5N1 strains, combined with careful, systematic laboratory-based monitoring, is essential.

Joseph-Charles J *et al* (2007)., [27] Oseltamivir phosphate (OP) is an antiviral drug that is used in the treatment and prophylaxis of both influenza A and influenza B. It is effective against all known influenza viruses than can infect humans, including pandemic influenza viruses and may be the most appropriate antiviral option against avian influenza caused by H5N1 virus. Tamiflu, the registered trademark used under exclusive license by Roche laboratories with OP as active pharmaceutical ingredient, is considered the best treatment for the bird flu disease. A simple, selective, linear, accurate and precise HPLC method was developed and validated for rapid assay of OP aimed to the quality control of Tamiflu capsules and generic versions. Isocratic elution

at a flow rate of 1.2 mL/min was employed on a Zorbax CN column (150 mm x 4.6mm; 5 microm) at ambient temperature. The mobile phase consisted of methanol and 0.04 M formic acid pH 3.0 (50:50, v/v). The UV detection wavelength was 226 nm and 20 microL of sample was injected. Sotalol hydrochloride was used as the internal standard (IS). The retention times for OP and IS were 3.40 and 2.25 min, respectively. The method was successfully applied to commercial pharmaceuticals, Tamiflu and generic versions. The proposed method could be applicable for routine analysis of OP and monitoring of the quality of marketed drugs as possibly counterfeit Tamiflu.

Hill G *et al* (2002).,[28] Oseltamivir is an ester prodrug of the active metabolite [3R,4R,5S]-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (Ro 64-0802), a potent and selective inhibitor of neuraminidase enzyme of influenza virus. Oseltamivir is rapidly hydrolyzed by hepatic carboxyl esterases to Ro 64-0802, which is then exclusively excreted by glomerular filtration and active tubular secretion without further metabolism. In vivo and in vitro studies were conducted to evaluate the renal drug-drug interaction potential of oseltamivir. Crossover studies were conducted in healthy subjects in which oral oseltamivir was administered alone and coadministered with probenecid, cimetidine, or amoxicillin. Probenecid completely blocked the renal secretion of Ro 64-0802, increasing systemic exposure (area under the curve) by 2.5-fold, but no interaction was observed with cimetidine or amoxicillin. These in vivo data show that Ro 64-0802 is secreted via an organic anion pathway, but Ro 64-0802 does not inhibit amoxicillin renal secretion. In vitro effects of Ro 64-0802 on the human renal organic anionic transporter 1 (hOAT1) were investigated using novel Chinese hamster ovary cells stably transfected with hOAT1. Ro 64-0802 was found to be a low-efficiency substrate for hOAT1 and a very weak inhibitor of hOAT1-mediated transport of p-aminohippuric acid (PAH). Ro 64-0802 did not inhibit the hOAT1-mediated transport of amoxicillin. In contrast, probenecid effectively inhibited the transport of PAH, Ro 64-0802, and amoxicillin via hOAT1. These in vitro observations are consistent with the in vivo data, validating the usefulness of the in vitro system for evaluating such drug-drug interaction. The study results demonstrate that oseltamivir has a low drug-drug interaction potential at the renal tubular level due to

inhibition of hOAT1.

Gopal C.Gosh *et al* (2010).,[29]Oseltamivir phosphate(op;Tamiflu) is a prodrug of the anti-influenza neuraminidase inhibitor oseltamivir carboxylate(OC) and has been developed for the treatment and prevention of both A and B strains of influenza.The recent increase in OP resistance in influenza A virus(H1N1;commonly called" swineflu")has raised the questions about the wide spread use of tamiflu in seasonal epidemics and the potential ecotoxicologic risk associated with its use in the event of a pandemic.The objectives of this study were to develop an analytical method for quantitative determination of OC in sewage treatment plant(STP) effluent and receving river water,and to investigate the occurrence of OC in STP effluent and river water in japan during a seasonal flu outbreak.An analytical method based on solid- phase extraction followed by liquid chromatography-tandem mass spectrometry.using this method,we analysed samples from three sampling campaigns conducted during the flu season.Results demonstrate that the highest concentration of OC detected in STP discharge was 293.3ng/l from a conventional activated-sludge-based STP;however ,we detected only 37.9ng/l from an advanced STP with ozonation as a tertiary treatment.In the receiving river water samples,we detected 6.6-190.2 ng/L OC,during the peak of the flu season.And concluded OC is present in STP in effluent and river water only during the flu season.Ozonation as tertiary treatment in STP will substantially reduce the OC load in STP effluent during an influenza pandemic or epidemic.

ElenaA.Govorkal *et al (2001).,*[30] The orally administered neuraminidase(NA)inhibitor was tested in parallel with zanamivir and oseltamivir against a panel of avian influenza viruses for inhibition of NA activity and replication in tissue culture.The agents were then tested for protection of mice against lethal H5N1and H9N2 virus infection.In vitro,RWJ-270201was highly effective against all nine NA subtypes.NA inhibition by RWJ-270201(50% inhibitory concentration,0.9 to 4.3nM) was superior to that by zanamivir and oseltamivir carboxylate.RWJ-270201inhibited the replication of avian influenza viruses in MDCK cells(50% effective concentration,0.5 to 11.8µm).Mice given 10mg of RWJ-270201per kg of bodyweight per day were completely protected against lethal challenge with influenza A(H5N1) and(H9N2)viruses.Both RWJ-270201

and oseltamivir significantly reduced virus titers in mouse lungs at daily dosages of 1.0 and 10mg/kg and prevented the spread of virus to the brain.When treatment began 48hr after exposure to H5N1 virus,10mg of RWJ-270201 kg/day protected 50% of mice from death.These results suggest that RWJ-270201 is at least as effective as either zanamivir or oseltamivir against avian influenza viruses and may be of potential clinical use for treatment of emerging influenza viruses that may be transmitted from birds to humans.

Ashish Ashok Thatte *et al (2011).,* [31] Oseltamivir phosphate is used in the treatment and prophylaxis of both influenza A and influenza B.In present investigation two simple and sensitive extractive photometric methods have been developed and validated for the determination of Oseltamivir phosphate in bulk and capsule dosage form.The developed methods involve formation of extractable ion pair complex of drug with bromocresol green and bromocresol purple dyes in acidic medium.Chloroform is used as extracting solvent for Bromocresol green and Bromocresol purple.Extractable complexes shows maximum absorption at 416nm and 404.5nm and the drug shows linearity range for Bromocresol green and Bromocresol purple in concentration range of 8-28µg/ml.The coloured chromophores were found to be stable for 24hours.The effect of pH and dye concentration was also studied.

Zeynep Aydogmus *et al (2010).,* [32] A new,sensitive RP-HPLC method was developed for the determination of Oseltamivir phosphate in capsules and plasma.The method was based on the reaction of the drug with 4-chloro-7-nitrobenzofurazan in borate buffer solution of pH 8.50.Isocratic chromatography was performed on a C18 column with acetonitrile-10mM nitric acid as the mobile phase with Fluorescence detection.Mexiletine hydrochloride was used as an internal standard.Analytical parameters were evaluated.The calibration range was linear from 50.0-750.0ng/ml.The mean percentage recovery in capsules and plasma were 99.95% and 95.42% respectively.

Avramov-I.Ivicmilkal *et al* (2011).,[33] A gold electrode was applied in the voltametric determination of oseltamivir phosphate standard in 0.05M NaHCO3.Oseltamivir

phosphate as a standard and as a component of Tamiflu capsule exhibited the identical cyclic voltamogram.The peaks originated from excipients in capsule do not appear under the applied electrochemical conditions.The electrochemical method for the qualitative determination of Oseltamivir phosphate in Tamiflu capsule by cyclic voltametry was developed.The presence of Oseltamivir phosphate as standard and as a content of Tamiflu capsule in electrolyte as well as their concentrations were simultaneously checked by HPLC.The lack of the current/concentration dependency was established.The not pretreated glassy carbon electrode cannot be used for the determination of oseltamivir phosphate under identical experimental conditions presented for gold electrode

3. AIM AND OBJECTIVE OF THE STUDY

Aim :

- The main aim of the study is to formulate and evaluate Oseltamivir phosphate capsules 75 mg.

Objective :

- The objective of the present study is to develop a pharmaceutically equivalent, low cost, quality improved and stable formulation of Oseltamivir Phosphate capsules. Oseltamivir is an orally administered antiviral medication that selectively inhibits the influenza neuraminidase enzyme that are essential for viral replication.

Plan of the work :

It was planned to carry out study in the sequence below:

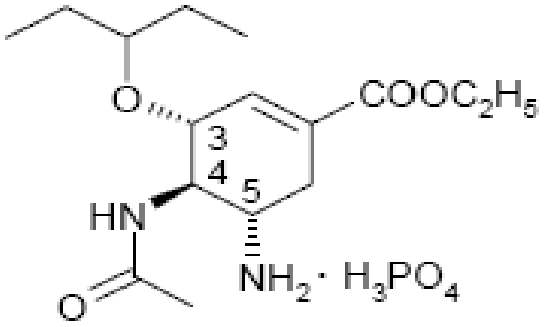
- Analysis of the dosage forms available in the market.
- Preformulation Studies**:** Solubility and compatibility of studies
- Formulation of Oseltamivir Phosphate capsules.
- Evaluation of Oseltamivir Phosphate capsules.
- Selection of the best formulation on the basis of *in vitro* drug release.
- Comparision of best formulation with that of innovator.
- Stability studies of Oseltamivir Phosphate capsules.

4.DRUG PROFILE

Oseltamivir phosphate [34,35,36,37]

Oseltamivir phosphate is an antiviral medication used to treat adults and children who have influenza (the flu)

Structure



Chemical formula	:	$C_{16}H_{28}N_2O_4$.
Chemical name	:	(3R,4R,5S)-4-acetylamino-5-amino3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid,ethyl ester, phosphate (1:1).
Molecular weight	:	312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.
Description	:	Oseltamivir phosphate is a white crystalline solid with a bitter taste.
Solubility	:	Freely soluble in water and methanol.
Category	:	Antiviral[NEURAMINIDASE INHIBITOR]
Density	:	1.22g/ml.
Bulk density	:	-0.15g/cm^3
pH value	:	3.3 to 5.3
Melting temperature	:	192 to 196°C
Melting point	:	201-203°C
Storage	:	stored at room temperature, 15-30 C (59-86 F).

Pharmacology

Oseltamivir is an antiviral drug, a neuraminidase inhibitor used in the treatment and prophylaxsis of both influenza A and influenza B.

Oseltamivir is a prodrug usually administered as phosphate, it is hydrolysed hepatically to the active metabolite, the free Carboxylate of Oseltamivir.

Mechanism of action

Oseltamivir is an ethyl ester requiring ester hydrolysis for conversion to the active form, Oseltamivir carboxylate. The proposed mechanism of action of Oseltamivir is inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Pharmacokinetics

Absorption and Bioavailability : Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of Oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to Oseltamivir carboxylate

Atleast 75% of an oral drug reaches the systemic circulation as Oseltamivir carboxylate. Exposure to Oseltamivir is less than 5% of total exposure after oral dosing.

Co-administration with food has no significant effect on the peak plasma concentration (551ng/ml under fasted conditions and 441ng/ml under fed conditions) and Area under curve (6218 ng.h/ml under fasted conditions and 6069 ng.h/ml under fed conditions) of Oseltamivir carboxylate.

Distribution

The volume of distribution (V_{ss}) of Oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

The binding of Oseltamivir carboxylate to human plasma protein is low (36%). The binding of Oseltamivir to human plasma protein is 42% which is significant to cause significant displacement base during interactions.

Metabolism

Oseltamivir is extensively converted to Oseltamivir carboxylate by esterase located predominently in the liver. Neither Oseltamivir nor Oseltamivir carboxylate is substrate for, or inhibitor of, cytochrome P450 isomers.

Elimination

Absorbed Oseltamivir is primarly (>90%) eliminated by conversion to Oseltamivir carboxylate.

Half life	:	1-3 hrs (Oseltamavir) 6-10 hrs (Oseltamavir carboxylate) Oseltamivir carboxylate is eliminated entirely (99%) by renal excretion.
Renal clearance	:	18.8 l/hr.
Glomerular	:	7.5 l/hr.
Filtration rate		Less than 20% of radio labelled dose is eliminated in feaces.
Dose	:	The recommended oral dose is 75 mg Oseltamivir twice daily for 5 days.
Strengths	:	30 mg, 45 mg and 75 mg.

Adverse effects

In treatment studies in adult and adolescents aged 13 years and older, the most frequently reported adverse effects were nausea and vomiting, diarrhea, bronchitis, abdominalpain, dizziness, headache, cough, insomnia, vertigo, fatigue.

In prophylaxis studies in adult and adolescent patients,adverse events were similar.

Other Drug interactions

- Four moderate drug interactions and three minor drug interactions,drug interactions of Oseltaltamivir phosphate.
- Alimta,Ampicillin/probencid,Baraclude(entecavir),Benemid(probencid), Entecavir,Flumist(influenza virus vaccine,live,trivalent)Premetrexed,Proben-c Probenecid and Colchicine.

Safety

It is contraindicated in patients who have had severe allergic reactions such as anaphylaxis or serious skin reactions such as toxic epidermal necrolysis,erythema

multiforme,serious bacterial infections may begin with influenza like symptoms or may co-exists withy or occur as complications during the course of influenza.

Storage

Protect from heat,light and humidity.

Excipient profile

Pregelatinised starch [38]

Nonproprietary Names

BP	:	Pregelatinised Starch
PhEur	:	Starch, Pregelatinised
USP-NF	:	Pregelatinized Starch
Synonyms	**:**	Insta-Starch, Amylum pregelificatum, compressible starch.
Chemical Name	:	Pregelatinized starch
Empirical Formula	:	$(C_6H_{10}O_5)_n$
Functional Category	**:**	Tablet and capsule diluents, tablet and capsule Disintegrant, tablet binder.

Applications in Pharmaceutical Formulation or Technology

Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,(Small LE et al., 1978) and disintegrant.

Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Typical Properties

Solubility	:	Practically insoluble in organic solvents.slightly soluble in cold water,depending on degree of pregelatinisation
Density (bulk)	:	0.586 g/cm3
Density (tapped)	:	0.879 g/cm3

Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules, suspensions, and tablets; vaginal preparations). Included in nonparenteral medicines licensed in the UK.

Croscarmellose Sodium [38]

Synonyms	**:**	Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Primellose; Solutab; Vivasol.
Chemical Name	:	Cellulose, carboxymethyl ether, sodium salt.
Empirical Formula	:	Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.
Functional Category	:	Tablet and capsule disintegrant
Description	:	Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Typical Properties

Density (bulk)	:	0.529 g/cm^3
Density (tapped)	:	0.819 g/cm^3
Solubility	**:**	Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material.

Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules,granules, sublingual tablets, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List ofAcceptable Non-medicinal Ingredients.

Povidone (Chowdary KP et al., 1995)[38,39]

Synonyms	:	Kollidon;Plasdonepolyvidone;
Chemical Name	**:**	1-Ethenyl-2-pyrrolidinone homopolymer polyvinylpyrrolidone; povidonum
Empirical Formula	:	$(C_6H_9NO)_n$
Functional Category :		Disintegrant; dissolution enhancer; suspending agent; tablet binder.
Description	**:**	Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourles spowder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Typical Properties

Density (bulk)	:	0.29–0.39 g/cm3.
Density (tapped)	:	0.39–0.54 g/cm3
Solubility	:	Freely soluble in acids, chloroform, ethanol(95%) ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.

Regulatory Status

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in non parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Talc [38]

Non proprietary Names

BP	:	Purified Talc
JP	:	Talc
PhEur	:	Talc
USP	:	Talc
Synonyms	:	Altalc; hydrous magnesium calcium silicate; Hydrous magnesium silicate; Imperial; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star, purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.
Chemical Name	:	Talc
Empirical Formula	:	$Mg_6(Si2O5)_4(OH)_4$
Functional Category	:	Anticaking agent; glidant; tablet and capsule diluent; capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. Talc is also used as a lubricant in tablet formulations;(Oetari RA., 2003) in a novel powder coating for extended-release pellets and as an adsorbant.

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Typical Properties

Solubility	:	Practically insoluble in dilute acids and alkalis, Organic solvents, and water

Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (buccal tablets; oral capsules and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients

Sodium stearyl fumerate [38,40]

Synonyms	:	Fumaric acid, octadecyl ester, sodium salt;natrii stearylis fumaras; Pruv; sodium monostearyl fumarate.
Chemical Name	:	2-Butenedioic acimd,onooctadecyl ester, sodium salt
Empirical Formula	:	$C_{22}H_{39}NaO_4$
Functional Category	:	Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.(Holzer AW et al., 1997). It is also used incertain food applications.

Description

Sodium stearyl fumerate is a fine, white powder with agglomerates of flat, circular-shaped particles.

Typical Properties

Density (bulk)	:	0.2–0.35 g/cm3
Density (tapped)	:	0.3–0.5 g/cm3
Solubility	:	Acetone Practically insoluble Chloroform Practically insoluble Ethanol Practically insoluble Methanol Slightly soluble

Regulatory Status

GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent in various bakery products, flour-thickened foods, processed cereals up to 0.2–1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Database (oral capsules and tablets)

5.METHODOLOGY

Table: 4 List of materials

Materials	Manufacturers
Oseltamivir phosphate	Msn pharmaceuticals,Hyderabad.
Pregelatinised Starch	Colorcorn Asia Pvt Ltd,Mumbai.
Croscarmellose sodium	Signet chemical corporation,Mumbai.
Povidone K-30	Signat chemical corporation,Mumbai.
Talc	Signat chemical corporation,Mumbai.
Sodium stearyl fumerate	J.R.S Pharma,Germany.

Table: 5 List of equipments

S.No.	Instruments Name	Manufacturer
1	Mechanical stirrer	Remi Mortors,Mumbai.
2	Tray Drier-TD6	Anchor Mark,Mumbai.
3	Tap Density Tester-ETD-1020	Electro Lab,Canada.
4	Electro Magnetic & Digital Shieve Shaker-EMS-8	Electropharma,Banglore.
5	Moisture Analyzer-HG63	Toledo,Germany.
6	Disintegration Tester-ED 2AL	Electro Lab,Canada.
7	Conta Bin Blender	Anchor Mark ,Mumbai.
8	Rapid Mixer Granualator-RMG25	Anchor Mark ,Mumbai.
9	Fluid Bed Drier(Small)	UMANG Pharma Tech, Maharastra.
10	Dissolution Tester USP-08L,12L	Electro Lab,Canada.
11	UV-VisibleSpectrophotometer	Agilent,Haryana.
12	Laboratory Oven	NSW INDIA,Haryana.
13	p^H Meter	Cyberscan, Banglore.
14	Laboratory Centrifuge Appratus-R4C	Remi,Mumbai.
15	Water Bath	Equitron,New Delhi.
16	Ultra Sonic Cleaner (Sonicator)	Enertech,Canada.
17	HPLC with dual λ absorbance detector 2487	Waters,United States.
18	HPLC with R.I.Detector 2414	Waters,United States.
19	HPLC with photo array detector 2996	Waters,United States
20	K.F. Titrator	Polymon,Japan.
21	Stability Chamber	Thermo Lab,India

Pre-formulation studies

Objective

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substances to formulate in to a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility, melting point, molecular weight, sieve analysis.

Physical Appearance

The appearance of the API was done by visual observation

Bulk Density:

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring presieved blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by Bulk density $=W/V_{0,}$

Bulk Density= Weight of the Blend/ Bulk Volume of the Blend

W=weight of powder, $V_{0=}$Initial volume

Tapped Density:

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Tapped Density=Weight of Blends/ Tapped Volume of Blends

Tapped density=W/Vf, W=weight of powder,F=final volume.

Carr's Index

Carr's Index is measured using the values of the bulk density and tapped density.

The following equation is used to find the Carr's index

CI=(TD-BD)/TD*100

Where, TD= Tapped Density, BD= Bulk Density

Table 6 Compressibility Index

Compressibility index	Type of flow
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

Angle of Repose:

The manner in which stresses are transmitted through a bed and beds response to applied stress reflected in the various angles of friction and response. The most commonly used of these is angles of response, which may be determined experimentally by a number of methods. The method used to find the angles of response is to pour the power in a conical heap on a level. Flat surface and measure the inclined angled with the horizontal pile.

$$\mathbf{Tan\theta} = \frac{h}{r}$$

Where h→Height of the heap

R → Radius of the heap.

Table 7 Angle of Repose

Angle of repose (degrees)	Flow property
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very, Very poor

Haussner's Ratio

Haussner's ratio was determined as the ratio between the tapped density to that of the bulk density.

Haussner's ratio= ρ_t/ρ_o

Where, ρ_t= Tapped Density,

ρ_0= Bulk Density.

Table 8 Haussner's Ratio

Haussner's ratio	Type of flow
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very Very poor

Compatibility studies

Samples were placed in 3 ml glass crimp-top ampoules. The reference cells were loaded with identical ampoules containing 200 mg of dry talc to balance the heat capacities. Before starting a series of experiments, all four calorimetric cells were calibrated using two-point static electrical calibration at 0 and 299.6µW. The samples and reference ampoules were sealed with fresh Teflon-lined closures just to starting the experiment and stored at 40°C,75%RH for 28 days and 55°C for 14 days.

COMPATIBILITY STUDIES FOR OSELTAMIVIR PHOSPHATE CAPSULES 75mg.

Table 9 Compatability studies of Oseltamivir phosphate capsules

S.NO	INGREDIENTS	RATIO	QUANTITY (gm)	2 WEEKS	4 WEEKS
1	Oseltamivir Phosphate	1	2	NI	NI
2	Pregelatinised starch	1	2	NI	NI
3	Croscarmellose sodium	1	2	NI	NI
4	Povidone K-30	1	2	NI	NI
5	Talc	1	2	NI	NI
6	Sodium stearyl fumerate	1	2	NI	NI
7	Oseltamivir Phosphate + Pregelatinised starch	1:0.5	4.5 : 2.07	NI	NI
8	Oseltamivir Phosphate + Croscarmellose sodium	1:0.1	6:0.6	NI	NI
9	Oseltamivir Phosphate + Povidone K-30	1:0.03	6:0.180	NI	NI
10	Oseltamivir Phosphate +talc	1:0.015	6:0.090	NI	NI
11	Oseltamivir Phosphate + Sodium stearyl fumerate	1:0.015	6:0.090	NI	NI

EVALUATION OF CAPSULES:

A.Weight variation test:

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be ± 5 %.

WEIGHT VARIATION OF FORMULATIONS

parameters	F 1	F2	F3	F4	F5	F6	F7
Weight variation(mg)	210	218.4	223.2	223.9	225.11	235.3	225.3

B. Content uniformity test:

The content of individual dosage complies with the test if not more than one individual content is outside the limits of 85 to 115 percent of the average content and none is outside the limits of 75 to 125 percent of the average content. The preparation fails to comply with the test if more than three individual contents are outside the limits of 85 to 115 percent of the average content or if one or more individual contents are outside the limits of 75 to 125 percent of the average content.

C. Lock length

It was tested by using vernier calipers.

LOCKED LENGTH OF FORMULATIONS

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Locking length(mm)	17.6	18	18	18	18	18	18

D. Moisture permeation test:

The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules. The degree and rate of moisture penetration is determined by packing the dosage unit together with a colour revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change (indicating desiccating absorption of moisture) and comparing the pre and post weight of the packaged unit and also by the Karl Fisher titration equipment.

E. Disintegration

The compendial disintegration test for hard and soft capsules follows the same procedure and uses the same apparatus as used for uncoated tablets. The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute in to a thermostatically controlled fluid at 37ºc and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

DISINTEGRATION TIME

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Disintegration time(min)	4.10	4.08	4.0	3.50	3.50	3.20	3.20

DISSOLUTION AND DISSOLUTION TESTING

DESIGN OF APPARATUS

The ideal features of a dissolution apparatus are

1. The fabrication, dimensions, and positioning of all components must be precisely specified and reproducible, run to run.

2. The apparatus must be simply designed, easy to operate, and useable under a variety of conditions.

3. The apparatus must be sensitive enough to reveal process changes and formulation differences but still yield repeatable results under identical conditions

.

4. The apparatus, in most cases, should permit controlled variable intensity of mild, uniform, nonturbulent liquid agitation. Uniform flow is essential because changes in hydrodynamic flow will modify dissolution

.

5. Nearly perfect sink conditions should be maintained.

6. The apparatus should provide an easy means of introducing the dosage form into the dissolution medium and holding it, once immersed, in a regular reliable fashion.

7. The apparatus should provide minimum mechanical abrasion to the dosage form (with exceptions) during the test period to avoid disruption of the microenvironment surrounding the dissolving form.

8. Evaporation of the solvent medium must be eliminated, and the medium must be maintained at a fixed temperature within a specified narrow range. Most apparatuses are thermostatically controlled at around 37°C-38°C.

9. Samples should be easily withdrawn for automatic or manual analysis without interrupting the flow characteristics of the liquid. In the latter case, efficient filtering should be achieved.

10. The apparatus should be capable of allowing the evaluation of disintegrating, nondisintegrating, dense or floating tablets or capsules, and finely powdered drugs

11. The apparatus should allow good inter laboratory agreement.

There are two principal types of apparatus design. One is based on limited volume that is constrained to the size of the container used. The second type uses a continuous flow cell to house the dosage form and permits constant replenishment of the dissolution fluids.

Paddle Apparatus

An apparatus described by Levy and Hayes may be considered the forerunner of the beaker method. It consisted of a 400 ml beaker and a three-blade, centrally placed polyethylene stirrer (5 cm diameter) rotated at 59 rpm in 250 ml of dissolution fluid (0.1 N HCl). The capsule was placed down the side of the beaker and samples were removed periodically. In the pharmacopoeial apparatus 2—the paddle apparatus method— a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should position not more than 2 mm at any point from the vertical axis of the vessel and rotate without significant wobble. A distance of 25 ^ 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating to prevent corrosion. Again typical arrangements for the apparatus. The dosage form is allowed to sink to the bottom of the flask before rotation of the blade commences.

Sinkers are recommended to prevent floating of capsules and other floatable forms. A small, loose piece of nonreactive material (e.g., a few turns of wire helix) may be attached to the dosage form. Soltero et al. thoroughly examined the influence of sinker shapes on dissolution rates obtained from gelatin capsules. Although a stainless steel helix is officially recommended, alternative shapes can greatly affect the dissolution rates.

DISSOLUTION STUDIES

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a capsule to dissolve under specified conditions.

The dissolution test was carried out in USP apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15 30, and 45 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus	:	USP Apparatus Type II (Paddle)
Dissolution Medium	:	0.1N Hydrochloric acid
Volume	:	900 ml
Temperature	:	37 ± 2^0 C
Rpm	:	50
Sampling intervals (min)	:	5, 10, 15, 30 and 45

Assay of OSELTAMIVIR PHOSPHATE capsules [37]

Assay procedure

Solution A: Dissolve 6.8g of potassium dihydrogen phosphate in 980ml of water. Adjust with 1M potassium hydroxide solution to a pH of 6.0 and dilute with water to 1L.

Mobile phase : Methanol, acetonitrile, and solution A(245 : 135 : 620)

Diluent : Methanol, Acetonitrile and 0.01N phosphoric acid (245 : 135 : 620)

Standard solution : 1mg/ml of USP Oseltamivir phosphate RS in diluent.

Sample solution : Weigh the content of 20 capsules and mix. Prepare the equivalent of about 1mg of oseltamivir per mL, based on the label claim, by first dispersing a suitable portion of the powder in about 40% of the flask volume of the diluents, using an ultrasonic bath for about 20min, and diluting with diluents to volume. Centrifuge an aliquot of this solution, and use the supernatant.

CHROMATOGRAPHIC SYSTEM [37]

Detector	:	UV
Column	:	4.6 mm × 150mm ; packing L7
Column temp	:	Ambient
Flow rate	:	1.0 ml / min
Wave length	:	280 nm
Injection Size	:	15 µl
Run time	:	**60min**

System suitability

Sample : Standard solution

Suitability requiremennts

The test is not valid unless the tailing factor is not more than 2.0, the column efficiency is not less than 2000 theoretical plates and the relative standard deviation for replicate injection is not more than 2.0 percent.

Analysis

Samples : Standard solution and sample solution

Calculate the percentage of $C_{16}H_{28}N_2O_4$ in the portion of capsule taken

$$\textbf{Result} = (r_u/r_s) \times (c_s/c_u) \times (M_{r1}/M_{r2}) \times 100$$

Where

r_u = Peak response from the sample solution

r_s = Peak response from the standard solution

c_s = Concentration of Oseltamivir in the sample solution (mg/ml)

c_u = Concentration of oseltamivir in the sample solution (mg/ml)

M_{r1} = Molecular weight of oseltamivir, 312.40

M_{r2} = Molecular weight of oseltamivir phosphate, 410.40

Acceptance criteria = 90.0 % - 110.0 %

ASSAY

parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Assay(%)	88.2	87.1	93.5	95.4	99.8	97.6	99.6

Stability Study:[42]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf-life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behaviour and properties of the drug substances and formal stability studies on the drug substance. Specification which is list of tests, references to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria as mentioned in ICH guide lines

PROCESS FLOWCHART

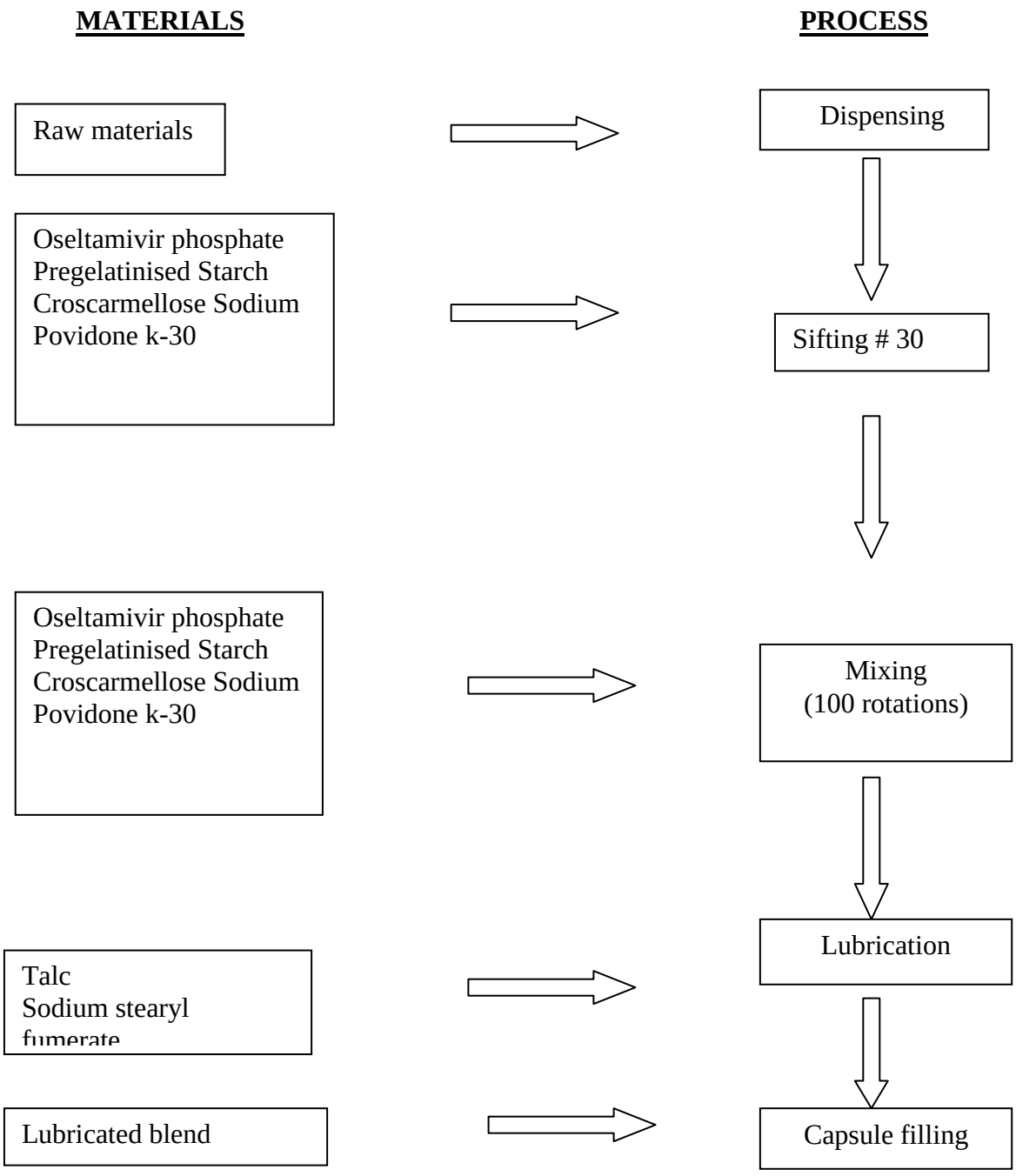


Table 10 Formulation of Oseltamivir phosphate capsules

SNO	INGREDIENTS	mg/capsule						
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	Oseltamivir phosphate	98.5	98.5	98.5	98.5	**98.5**	98.5	98.5
2	Microcrystalline cellulose(101)	40	38	-	-	**-**	-	-
3	Pregelatinised starch	-	-	48.5	46.2	**45.5**	44.5	45.5
4	Croscarmellose sodium	7.5	7.5	7.7	10	**10**	10	10
5	Povidone K-30	8	10	2.3	2.3	**3**	3	3
6	Sodium stearyl fumerate	3	3	1.5	1.5	**1.5**	2	1.5
7	Talc	3	3	1.5	1.5	**1.5**	2	1.5
8	Purified water	q.s	q.s	-	-	**-**	-	-

- 98.5mg of Oseltamivir phosphate ≈ 75 mg of Oseltamivir

Wet granulation method (F1 & F2)

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Procedure

1. The active ingredient and excipients are weighed and mixed.
2. The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin, and povidone.
3. Screening the damp mass through a mesh to form pellets or granules.
4. Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
5. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process

Dry blending process (F3 to F7) [43]

A dry, free-flowing mixture of resin with plasticizers and other additives prepared by blending the components under high shear at temperatures below the fluxing point. Dry blends are generally more economical than molding powders and pellets made by plasticating and extrusion.

The dry blending process begins with the receipt of the ingredients. The ingredients are typically stored until they are tested for conformance to specifications,including microbiological contamination. Since microbiological contaminants may be present in low numbers and may be non-randomly distributed within the lot, it is difficult to assure microbiological quality by lot testing alone. Therefore, manufacturers of dry-blended products try to develop and maintain close relationships with their ingredient suppliers. Each supplier must produce their product in a manner that assures that harmful bacteria will not contaminate the finished ingredient. This is usually accomplished by a combination of appropriate process controls and strict adherence to good manufacturing practices.

Dry ingredients are blended in large batches (1, 000 to 5,000 lbs.) in a ribbon blender or other large scale blending equipment. The ingredients must be blended until the nutrients are uniformly distributed throughout the batch. The blended product is then passed through a sifter to remove oversize particles and extraneous material. The sifted product is then transferred to bags, totes or lined fibre board drums for storage. In some cases, the powder is transferred directly to the powder packaging line. At the packaging line, the powder is transferred to a filler hopper that feeds powder into the can filling line. Filled cans are flushed with inert gas, seamed, labelled, coded and packed into cartons. Typically, finished product is held until it undergoes a final check for conformance to specifications, including testing for microbiological contaminants.

RESULTS AND DISCUSSION

Determination of Flow properties

Table :10 Formulation parameters of formulated physical mixtures of drug and excipient

Formulation	Blend Characterisation				
	Angle of Repose(θ)	**Tap density(gm/ml)**	**Bulk density(gm/ml)**	**Carr's index(%)**	**Haussner's ratio**
F1	33.4±0.08	0.675±0.04	0.529±0.04	31.60±0.51	1.12±0.03
F2	31.7±0.12	0.675±0.49	0.53±0.05	32.53±0.14	1.12±0.04
F3	34.1±0.06	0.657±0.02	0.526±0.05	33.47±0.16	1.13±0.02
F4	35.8±0.08	0.675±0.034	0.543±0.05	33.84±0.12	1.15±0.05
F5	29.5±0.08	0.712±0.12	0.608±0.2	29.55±0.04	1.10±0.02
F6	29.8±0.06	0.627±0.021	0.627±0.021	28.62±0.08	1.12±0.06
F7	29.4±0.05	0.663±0.025	0.552±0.04	28.74±0.04	1.09±0.05

Table . 12: *In-vitro* dissolution profile of F1

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	64.2	68.8
2	10	74.3	90.9
3	20	79.8	95.4
4	30	84.5	96.0

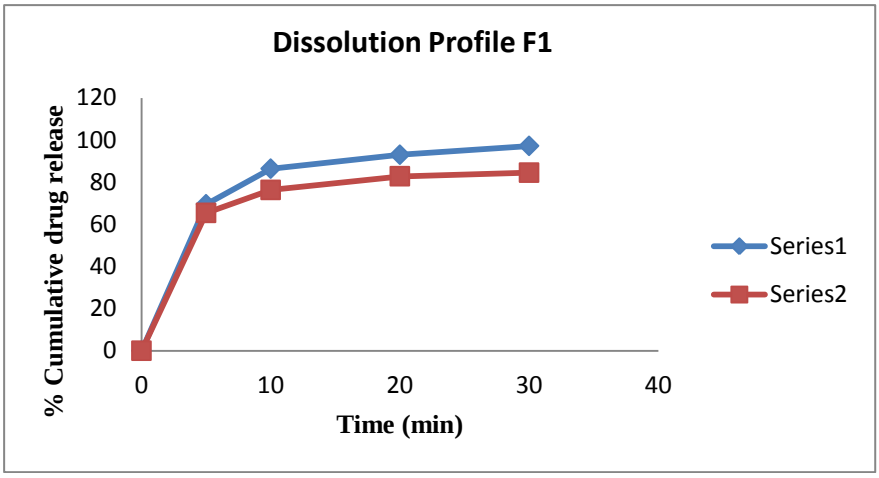


Figure:3 Dissolution profile of F1

Discussion : In this F1 Wet granulation process was employed by using MCC (101) grade. Required fill weight of the capsule was not achieved in this trial

Table . 13: *In-vitro* dissolution profile of F2

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	65.4	68.8
2	10	75.9	90.9
3	20	80.1	95.4
4	30	82.6	96.0

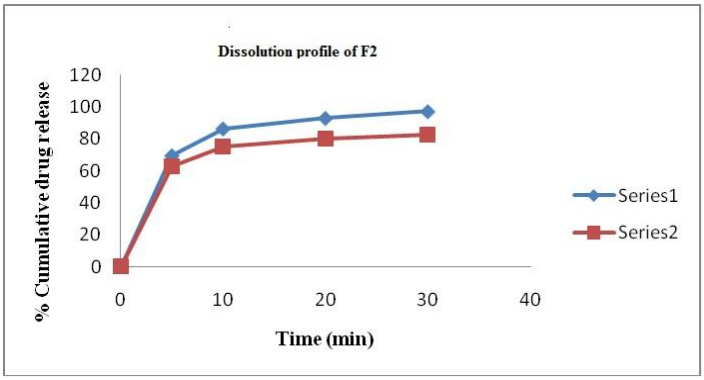


Figure:4 Dissolution profile of F2

Discussion : In this F2 Wet granulation process was employed by using MCC (101)grade. Required fill weight of the capsule was achieved but the assay anddissolutionvalues are very low.

Table . 14: *In-vitro* dissolution profile of F3

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	68.2	68.8
2	10	76.0	90.9
3	20	86.8	95.4
4	30	92.2	96.0

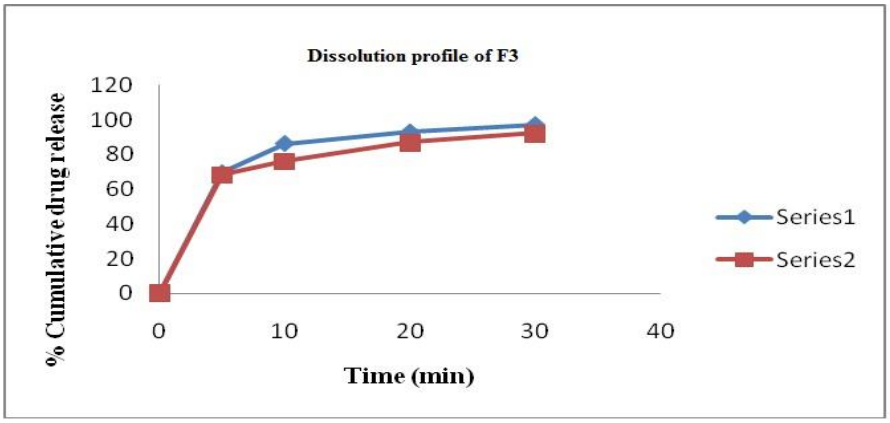


Figure:5 Dissolution profile of F3

Discussion : The process is changed from Wet granulation to direct filling of dry blend in to capsules. Pregelatinised starch is used. Dissolution and Assay values are better when compare to wet granulation

Table . 15: *In-vitro* dissolution profile of F4

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	70.2	68.8
2	10	82.5	90.9
3	20	87.4	95.4
4	30	94.8	96.0

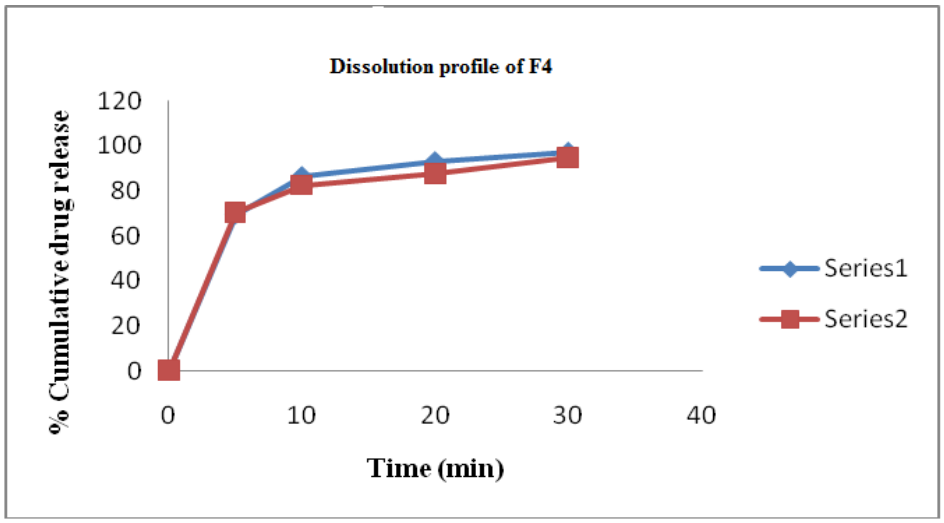


Figure:6 Dissolution profile of F4

Discussion : In F4 the Dissolution and Assay values were greater than the previous formulation but not matches with that of reference formulation

Table . 16: *In-vitro* dissolution profile of F5

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	78.6	68.8
2	10	96.4	90.9
3	20	98.2	95.4
4	30	99.7	96.0

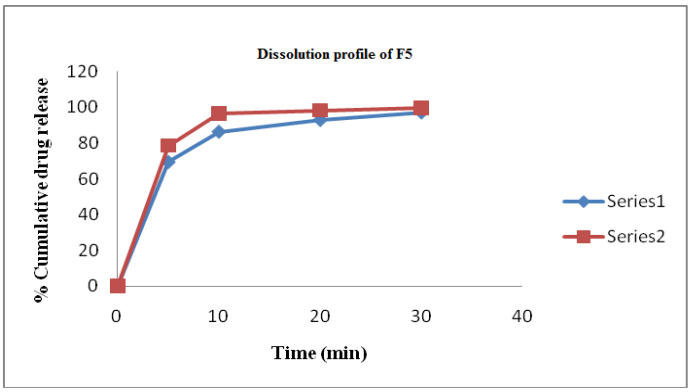


Figure:7 Dissolution profile of F5

Discussion : In this F5 the Dissolution and Assay values were greater than the previous formulation and shows better results than that of reference formulation.

Table . 17: *In-vitro* dissolution profile of F6

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	76.5	68.8
2	10	89.8	90.9
3	20	96.6	95.4
4	30	97.4	96.0

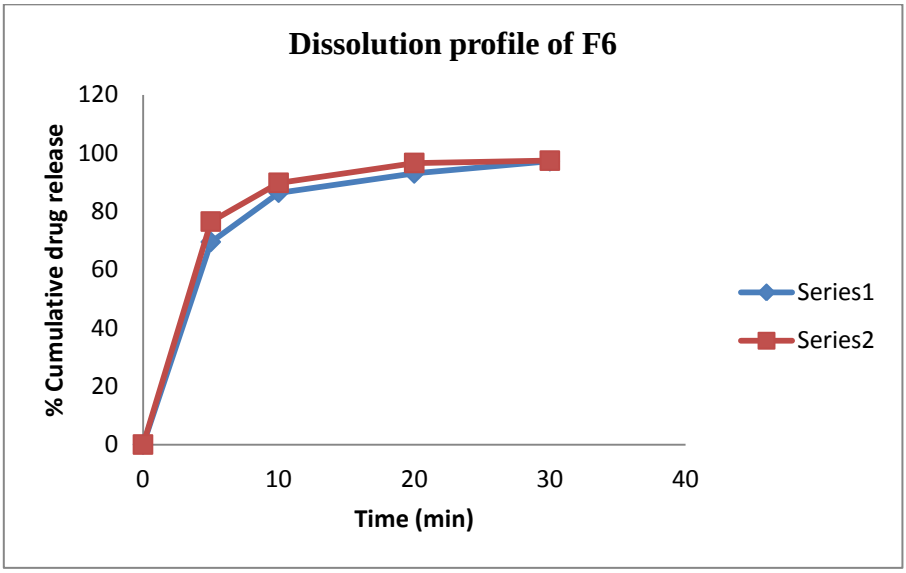


Figure:8 Dissolution profile of F6

Discussion : In this F6 both the glidants concentration were increased to higher concentration levels. There is no much variation in the Dissolution and Assay values to that of the reference formulation

Table No. 18: *In-vitro* dissolution profile of F7

SNO	TIME(Min)	% CDR	%CDR OF INNOVATOR
1	5	74.4	68.8
2	10	96.7	90.9
3	20	97.9	95.4
4	30	99.5	96.0

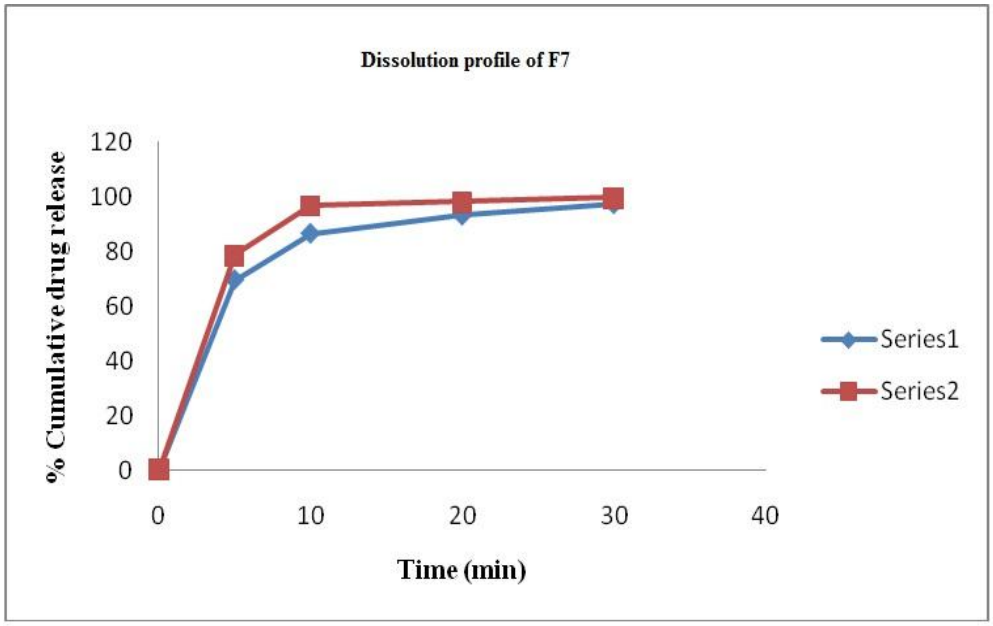


Figure:9 Dissolution profile of F7

Discussion : In this F7 batch size of the capsules were increased and the reproducibility of results to that of F5 were seen.

IDENTIFICATION OF OSELTAMIVIR PHOSPHATE BY IR SPECTROSCOPY

The experimental work stated with raw material analysis of Oseltamivir phosphate was identified by infrared spectral analysis .the report was given below.

Figure-12 FTIR SPECTRUM OF OSELTAMIVIR PHOSPHATE STANDARD

Method:KBR

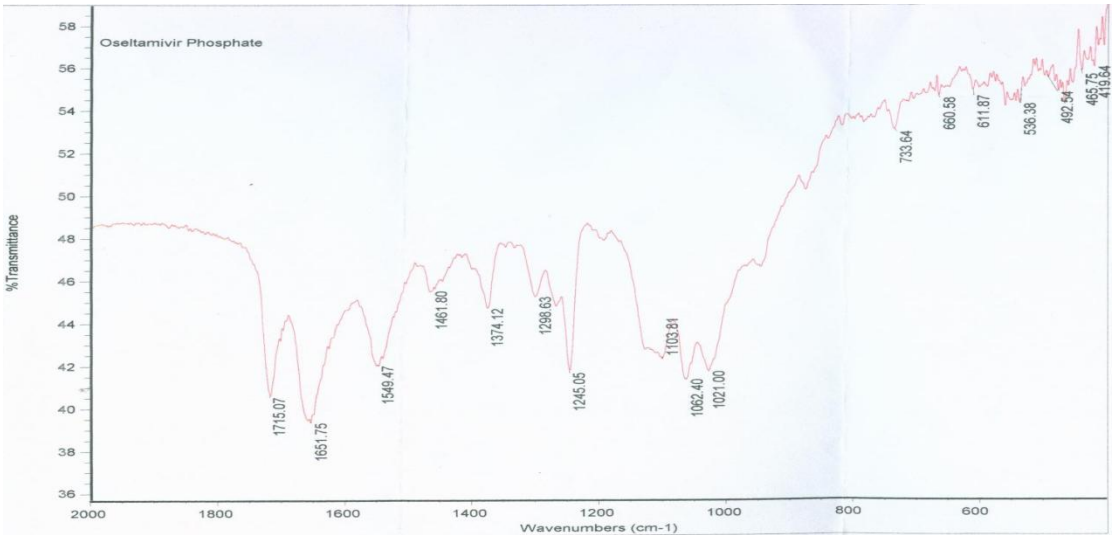


Figure-13 FTIR SPECTRUM OF OSELTAMIVIR PHOSPHATE API

Method:KBR

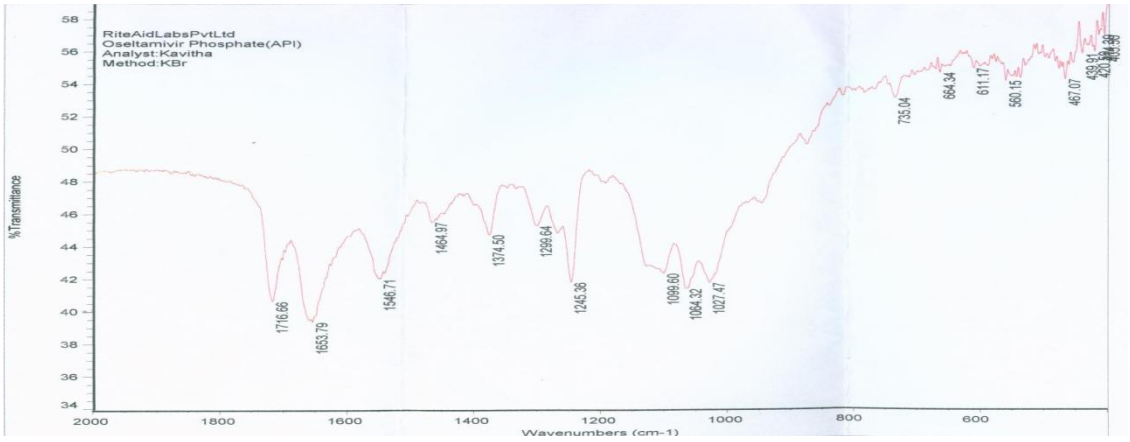
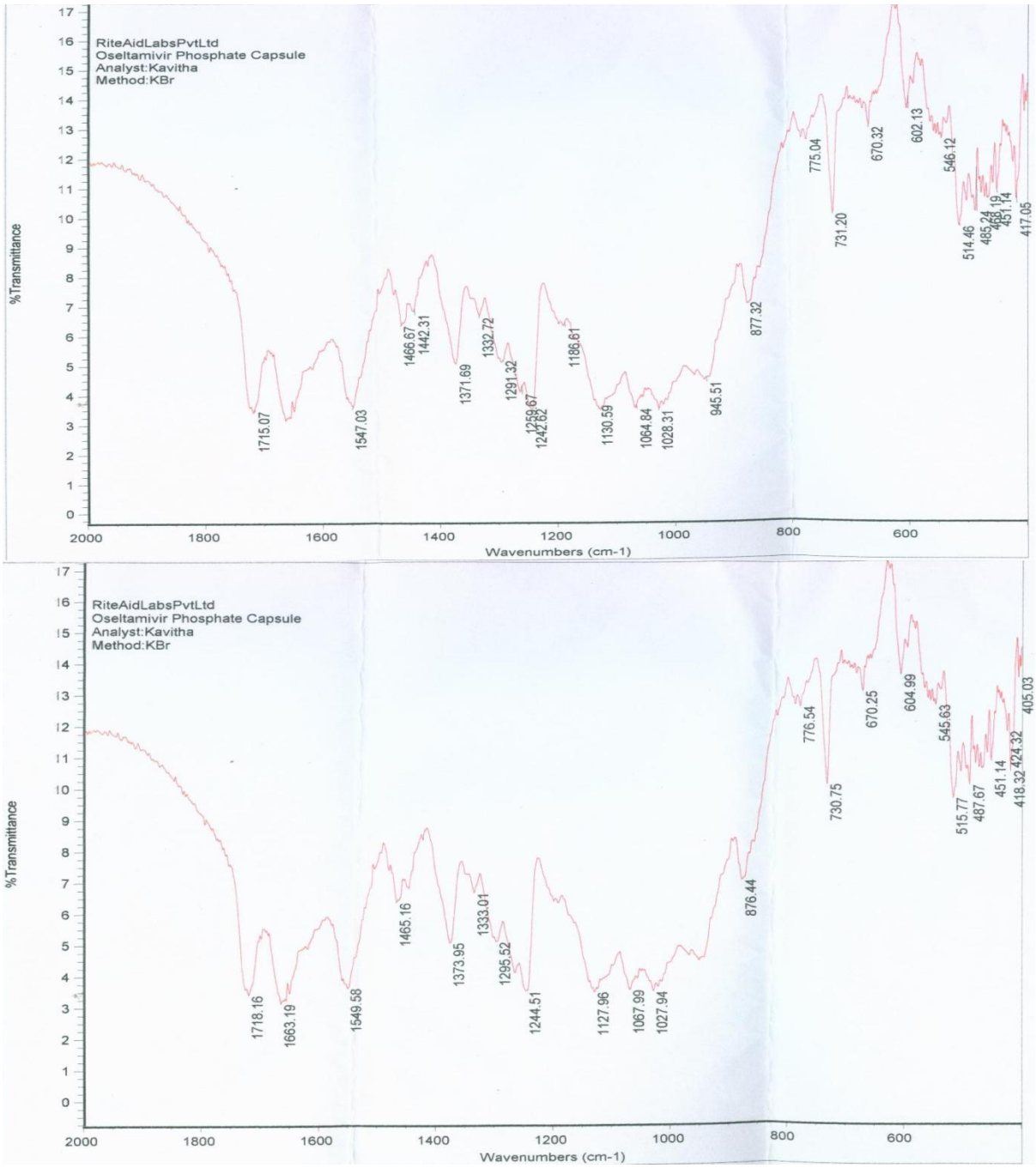


Figure-14 COMPATIBILITY STUDIES OF OSELTAMIVIR PHOSPHATE WITH EXCIPIENTS

Method:KBR



The IR peaks in the both,oseltamivir phosphate before compatibility and after compatibility,were found to be nearly same so the excipients were compatible with the drug.The correlation of the both the spectrum shows the compatibility of the drug with the excipients used.

TABLE:19 STABILITY STUDIES

SNO	TEST	RESULTS				
		STORAGE CONDITIONS				
		40°c/75%RH				**25 °c/ 60%RH**
		INIT IAL ANALYSIS	IST MONTH	2ND MONTH	3RD MONTH	3RD MONTH
1	Description	Carmel/pink coloured size 2 capsules containing white to off white granular powder	Carmel/pink coloured size 2 capsules containing white to off white granular powder	Carmel/pink coloured size 2 capsules containing white to off white granular powder	Carmel/pink coloured size 2 capsules containing white to off white granular powder	Carmel/pink coloured size 2 capsules containing white to off white granular powder
2	Identification	Complies	Complies	Complies	Complies	Complies
3	Water content		2.80%	3.56%	4.38%	3.13%
4	Assay		101.60%	100.30%	99.00%	99.10%
5	Dissolution		98.9	103.6	98.2	105.6
6	Related substances					
	% of impurity A		0.04%	0.08%	0.08%	0.03%
	% of impurity B		0.09%	0.09%	0.08%	0.01%
	% single max unknown impurity		0.02%	0.03%	0.04%	0.10%
	% of total impurity		0.18%	0.29%	0.40%	0.19%

STABILITY STUDIES:

The purpose of stability studies is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature ,humidity etc

OBJECTIVE

To generate documented evidence that the tablets manufactured comply with the finished product signification s under accelerated and long term stability conditions

DESIGN PLAN

ACCELERATED STUDY:-the product is subjected to accelerated stability studies at 55°c for 2weeks and 40°c ±5%RH for 6months

LONG TERM STUDY:-

The product is subjected to long term studies at 25^0 c± 2^0 c/60%±5%RH for 12 months

PACKAGE TYPE:-

The tablets were packed as 30's count in HDPE containers,induction sealed with adsorbent cotton

TaBLE:20 SAMPLING WITH DRAWAL SCHEDULE

s.no	Storage condition	Test period
1	40°C±2°C/75%±5%RH	1month
		2month
		3month
2	25°C±2°C/60%±5%RH	3months

Related compounds

A.(3S,4R,5s)-ethyl 4- acetamido-5-amino-2- azido-3(pentan-3-yloxy) cyclohexane carboxylated **B**. Tri butyl phospine oxide.

9. SUMMARY

The purpose of the present study was to develop and characterize a generic product of Oseltamivir phosphate capsules of strength 75mg comparable to the innovators product.

Dry blending process was chosen to develop a finished pharmaceutical product Various formulation trials (F1-F7) were taken. In these trials, Drug: Excipient ratio was varied and the effect of Diluent, Disintegrant and Lubricant on the performance of both blend as well as on the physical and chemical parameters were studied.

Formulation F1 was carried out by using Microcrystalline cellulose(101) as diluents through Wet granulation process but the required fill weight of the capsules were not achieved. In F2 formulation the capsule fill weight was achieved by altering the concentration of the diluents and the binder.In F3-F7 formulations dry blending process were employed and the Pre-gelatinised starch were used. In F3-F4 formulations the assay and dissolution were not satisfactory.In F3-F5 formulation the amount of Pre-gelatinised starch and crosscarmellose sodium were altered.In this F5 formulation good results were achieved when compared to that of the reference product.In F6 formulation the glidant concentration were increased but there is no variation in the results.In F7 formulation reproducibility of results were observed with the large batch size.

The formulation F5 were considered as the optimised trial of all the trials. The Dissolution and Assay results of F5 were good when compared with the reference product. . The batch F5 was loaded for long term and accelerated stability studies at 25 ± 2°C/60±5% RH and 40±2°C/75±5% RH. The results of stability data for 1st and 2nd and 3rd month were found to be good.

10. CONCLUSION

Oseltamivir phosphate is widely used as Anti-viral agent. They are formulated as Oseltamivir phosphate capsules which show better patient acceptability and compliance as conventional dosage forms.

Based on various studies carried out we arrived at the following conclusions:

Dry blending process was the preferred technology for the preparation of Oseltamivir phosphate capsule.

Based on the preliminary studies various formulation trials (F1-F7) were carried out with different concentrations of disintegrants, lubricants. From the various formulations it was concluded that the formulation batch of F5 was finalised as the optimized formula.

Formulation F5 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when compared with the marketed product. When subjected to accelerated stability studies the capsules were found to be stable.

Infrared spectrum of the sample was found to be in compliance with the spectrum obtained from reference sample.The spectrum of reference of oseltamivir phosphate shown in figure no:12,and the spectrum of reference of sample of oseltamivir phosphate shown in figure no:13.Both show the characteristic transmittance in the range of 1800 cm^{-1} to 2000$cm^{-1.}$

Compatibility studies with Excipients;

The physical observation had shown that there is no colour change in all conditions,It shows there is no interaction in figure 14,shows that the FTIR spectra of plain oseltamivir phosphate and oseltamivir phosphate with excipients.

6.BIBLIOGRAPHY

1. Leon Lachman., Herbert A. Liebernan., Joseph L. Kanig. The theory and Practice of Industrial Pharmacy, third ed. Varghese Publishing house, Bombay,1991, 374-375.
2. Loyd V Allen,r. Nicholas G. Popovich Howard C. Ansel. Manufacturing of Hard gelatin capsule shells, eighth edition. 2008 , 206-208.
3. http://www.pharmpedia.com/Hard_Gelatin_Capsules
4. Botzolakis JE., Augsburger LL. Disintegrating agents in hard gelatincapsules. Drug Development Industrial pharmacy .,1998, 14, 29–41.
5. http://www.brair.com/files/app_updates/SoftGelatinCapsuleManufacturing.pdf
6. http://www.freepatentsonline.com/5254294.html
7. http://www.rjengineering.com/process.htm
8. Small LE., Augsburger LL. Aspects of the lubrication requirements for an automatic capsule filling machine. Drug Development and Industrial Pharmacy., 1978, 4, 345–372.
9. Influenza-wikipedia,the free Encyclopedia
10. U.S.Food and Drug Administration
11. http://www.sciencedaily.com/antiviraldrug_htm
12. http://www.medicinenet.com/script/main/hp.asp
13. Tripati ,5 edition,725-726
14. H.P.Rang,M.M.Dale,5 edition,655
15. G Hoffmann-La Roche Inc. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations.'j Antimicrob chemother., 2010, 2, 5-10

16. Osato H., Jones IL., Chen A., Chai CL. Efficient formal synthesis of oseltamivir phosphate (Tamiflu) with inexpensive D-ribose as the starting material. Organic Letters.,2010, 12, 60-3.

17.Lindeman.,Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir,US national library of medicine national institute of health,2008,31(12)

18 Laborde-Kummer E., Gaudin K., Joseph-Charles J., Gheyouche R., Boudis H., Dubost JP. Development and validation of a rapid capillary electrophoresis method for the determination of oseltamivir phosphate in Tamiflu and generic versions. J Pharm Biomed Anal., 2009, 3, 544-6.

19. Ogihara T., Kano T., Wagatsuma T., Wada S., Yabuuchi H., Enomoto S., Morimoto K., Shirasaka Y., Kobayashi S., Tamai I. Oseltamivir (tamiflu) is a substrate of peptide transporter 1. Drug Metabolism and Disposition., 2009, 37, 1676 -1681.

20.Nie LD., Shi XX., Ko KH., Lu WD. A short and practical synthesis of oseltamivir phosphate (Tamiflu) from (-)-shikimic acid. Journal of Organic Chemistry., 2009, 74: 3970-3973.

21.Aydoğmuş Z. Simple and sensitive spectrofluorimetric method for the determination of oseltamivir phosphate in capsules through derivatization with fluorescamine. J Fluoresc., 2009, 19, 673-9.

22.Gong J., Xu W. Different synthetic strategies of oseltamivir phosphate: a potent influenza neuraminidase inhibitor. Curr Med Chem., 2008, 15, 3145-59.

23.Zutter U., Iding H., Spurr P., Wirz B. New, efficient synthesis of oseltamivir phosphate (Tamiflu) via enzymatic desymmetrization of a meso-1,3-cyclohexanedicarboxylic acid diester. Journal of Organic Chemistry.,2008, 73, 4895-902.

24.Ono H., Nagano Y., Matsunami N., Sugiyama S., Yamamoto S., Tanabe M. Oseltamivir, an anti-influenza virus drug, produces hypothermia in mice. Biological and pharmaceutical bulletin., 2008, 31, 638-42.

25. Gholamreza Bahrami,Baharesh mohammadi,Amirkiani.Determination of oseltamivir carboxylic acid in human serum by solid phase extraction and high performance liquid chromatography with uv detection,864,1-2, 38-42.

26. Aoki FY., Boivin G., Roberts N. Influenza virus susceptibility and resistance to oseltamivir.' Antiviral Therapy., 2007, 12, 603-16.

27.Joseph-Charles J., Geneste C., Laborde-Kummer E., Gheyouche R., Boudis H., Dubost JP.Development and validation of a rapid HPLC method for the determination of oseltamivir phosphate in Tamiflu and generic versions. Journal of Pharmaceutical and Biomedical Analalysis., 2007, 44, 1008-13.

28.Hill G., Cihlar T., Oo C., Ho ES., Prior K., Wiltshire H., Barrett J., Liu B., Ward P.The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metabolism and Disposition.,2002, 30, 13-9.

29.Gopal C.Gosh, Oseltamivir carboxylate,the active metabolite of oseltamivir phosphate (Tamiflu);detected in sewage discharge and river water in japan,The national institute of environmental health sciences;January 2010, 118,103-107

30.Elena A.govorkoval,Irina A.leneval,Olga G.Golubeva,Karen bush,Robert G.webster,comparision of RWJ-270201,zanamivir,and oseltamivir against H5N1,H9N2,and other avian influenza viruses,Antimicrob.Agents chemother; 2001,45.

31.Ashish Ashok Thatte,Pramila T,Simple extractive colorimetric determination of oseltamivir phosphate by Ion-pair complexation method in bulk and capsule dosage form,International journal of research in pharmaceutical and biomedical sciences;April-june 2011, 2(2), 543-547,

32.Zeynep Aydogmus,senacaglar,sidikatoker,RP-HPLC method for determination of oseltamivir phosphate in capsules and spiked plasma,Analytical letters,12 August 2010, 43,14, 2200-2209.

33.AvramovIvicmilkal,petrovicSlobodan,mijindusanz,Thequalitativedetermination of oseltamivir phosphate in Tamiflu capsule by cyclic voltammetry,Hemijska industrija, 2011, 6 :1,87-91

34. Drugs.com

35. http://www.rxlist.com/tamiflu-drug.htm

36. Drug.ca/drugs/db112

37. Indian pharmacopeia, 2010,3,1828-182

38. Raymomd C Rowe., Paul J Sheskey., Marian E Quinn. Hand book of pharmaceutical Excipients, sixth ed. American Pharmaceutical Association, Pharmaceutical Press, London, Washington,2009.

39. Chowdary KP., Ramesh KV. Microencapsulation of solid dispersions of nifedipine – novel approach for controlling drug release. Indian Drugs.,1995, 32, 477–483

40. Holzer AW., Sjogren J. Evaluation of sodium stearyl fumarate as a tablet lubricant. International Journal of Pharmaceutics; 1979, 2: 145–153.

41. Rudnic. Evaluations of the mechanism of disintegrant action. Drug Developement and Industrial Pharmacy., 1982, 8: 87–109.

42. ICH guide lines

43. http://www.thefreedictionary.com/Blending.